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EDITORIAL

Dear Colleagues,

It is with immense pleasure that we present the January 2026 issue of the Journal of Controversies in Obstetrics & Gynecology and Pediatrics, published under the auspices of the Medihealth Academy. This issue marks the first publication of the new year and reflects our ongoing commitment to advancing scientific knowledge in the fields of obstetrics, gynecology, and pediatrics.

Since its establishment, the Journal of Controversies in Obstetrics & Gynecology and Pediatrics has aimed to provide a scientific platform for evidence-based research and critical discussion of debated clinical topics. In rapidly evolving areas of medical practice, the careful examination of complex and controversial issues remains essential for improving patient care and supporting informed clinical decision-making.

The January 2026 issue presents focused yet diverse scientific content. It includes original research articles and review papers addressing pathological conditions encountered during pregnancy, a contribution exploring the use of artificial intelligence in the management of challenges within the pregnant population, and case reports from the pediatric patient group. Collectively, these contributions reflect both current clinical concerns and emerging perspectives relevant to everyday practice.

The journal maintains its established policy of publishing in English in order to support international visibility and scholarly exchange. This ongoing approach ensures that the scientific work of our authors remains accessible to a global audience of clinicians, researchers, and educators.

We would like to express our sincere appreciation to the authors for their valuable contributions, to the reviewers for their careful and constructive evaluations, and to the editorial team for their dedication throughout the publication process. Their combined efforts are fundamental to maintaining the scientific standards of the journal.

We invite researchers and healthcare professionals to contribute to future issues and to engage in the scholarly dialogue fostered by the Journal of Controversies in Obstetrics & Gynecology and Pediatrics. Through critical inquiry, multidisciplinary collaboration, and innovation, we aim to continue shaping the future of obstetrics, gynecology, and pediatrics.

Thank you for your continued support.

Sincerely,

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Journal of
Controversies in Obstetrics & Gynecology and Pediatrics

Volume: 4 Issue: 1 Year: 2026

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Journal of
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Original Article

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Simulation-based analysis of AI responses to sexual myths during pregnancy

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ABSTRACT

Aims: This study aimed to evaluate the quality, scientific accuracy, and communication characteristics of Artificial Intelligence generated responses to common sexual myths during pregnancy using a simulation-based approach.

Methods: Ten simulated patient questions reflecting widespread, non–evidence-based beliefs about sexual activity during pregnancy were deliberately constructed based on themes frequently reported in the literature. These questions addressed fetal perception, physical harm, developmental consequences, and moral or religious concerns. Responses generated by ChatGPT were analyzed qualitatively according to predefined criteria, including scientific accuracy, internal consistency, communication tone, and potential clinical risk. No real patient data were used, and no human subjects were involved.

Results: All responses were found to be broadly consistent with established obstetric and fetal physiology principles. The system consistently provided clear, reassuring, and nonjudgmental explanations, particularly for concerns related to fetal safety. However, individualized obstetric risk factors were rarely emphasized, which may limit clinical applicability in certain high-risk contexts. Responses to morally or culturally sensitive questions demonstrated a cautious and neutral communication style.

Conclusion: Artificial Intelligence generated responses may serve as a supportive informational tool for addressing common sexual myths during pregnancy. While scientifically accurate and communicative, such systems should not replace individualized clinical counseling. Their greatest value may lie in complementing physician–patient communication by identifying prevalent misconceptions and facilitating early educational interventions.

Keywords: Pregnancy, sexual behavior, Artificial Intelligence, health communication, medical myths

INTRODUCTION

Pregnancy is a period during which women and couples experience not only physiological changes but also numerous questions and uncertainties regarding sexual life. The safety of sexual intercourse during pregnancy for both the mother and the fetus, the boundaries of sexual activity, and potential risks are among the most frequently questioned topics in the literature.[1-3] It has been demonstrated that misconceptions and myths related to sexual activity during pregnancy are common and that these beliefs may negatively affect sexual satisfaction for both women and their partners.[4-7]

The presence of sexual myths during pregnancy is not limited to individual experiences but is closely associated with cultural, social, and educational factors.[8-10] Studies conducted in various societies have reported a high prevalence of scientifically unfounded beliefs, such as the assumption that sexual intercourse during pregnancy may harm the baby, cause preterm birth, or be morally inappropriate.[2,5,6] These misconceptions may become further reinforced in the absence of adequate communication with healthcare professionals.[11]

In recent years, individuals' health information seeking behaviors have increasingly shifted toward digital platforms. Online information sources and artificial intelligence–based conversational systems, in particular, allow users to ask health-related questions anonymously and rapidly.[12,13] Although Artificial Intelligence systems based on large language models have been reported to offer potential benefits in obstetric and gynecologic contexts, while promising, the accuracy and reliability of the information they provide remain subjects of ongoing debate.[14,15]

A limited number of studies evaluating Artificial Intelligence–generated responses to pregnancy-related questions have shown that, while responses are generally satisfactory, they may occasionally contain ethically inadequate, ambiguous, or potentially misleading information.[13,16] This concern

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is especially relevant in sensitive domains such as sexual health, where information that is inconsistent with scientific evidence may negatively influence individuals' perceptions and behaviors.[12] The World Health Organization has also emphasized the importance of ethical principles, accuracy, and reliability in the use of digital tools in healthcare.[17]

In this context, the present study did not use real patient data. Instead, simulated patient questions were deliberately constructed by the researchers to reflect commonly reported misconceptions and concerns in the literature. These questions were designed to represent prevalent myths or beliefs regarding sexual intercourse during pregnancy that conflict with scientific evidence or are frequently encountered in clinical practice. The aim was to evaluate the scientific accuracy, CAM and communication appropriateness of artificial intelligence–generated responses to these questions.[14-16]

The objective of this study was to examine Artificial Intelligence–generated responses to simulated questions reflecting common sexual myths during pregnancy and to analyze their consistency with current obstetric literature and adequacy in terms of health communication. The findings are expected to contribute to a better understanding of both the potential applications and the limitations of artificial intelligence–based systems in the field of women's health.

METHODS

Ethics

This study exclusively utilized publicly available and anonymized data extracted from ChatGPT interaction logs. No human subjects were involved, and no identifiable personal information was accessed. Therefore, institutional review board (IRB) approval was not required, in accordance with established ethical standards in digital health research. All procedures adhered to data privacy and confidentiality principles, ensuring that no individual user could be identified or linked to specific queries.

Study Design

This study is a qualitative, descriptive, and simulation-based analysis aimed at evaluating Artificial Intelligence–generated responses to questions reflecting common but scientifically unfounded beliefs regarding sexual activity during pregnancy. No real patients, patient relatives, or healthcare professionals were involved in the study. All queries were submitted using the same prompt structure and phrasing, without follow-up interactions. The analysis was conducted using a single model version available at the time of data collection, and all queries were executed within the same session to minimize variability related to temporal updates.

Data Source and Simulation Approach

The data analyzed in this study consisted of simulated patient questions deliberately constructed by the researchers to represent widely encountered myths about sexuality during pregnancy that are frequently reported both in the general use of ChatGPT (OpenAI) and in the existing literature. These simulated questions were structured to reflect common misconceptions, cultural taboos, and gaps in scientific knowledge related to sexual intercourse during pregnancy.[1,7] The ten questions used in this simulation were developed to reflect common sexual myths and misconceptions encountered during pregnancy. These questions were formulated based on routine clinical observations, frequently asked questions during obstetric counseling, and recurrent themes reported in patient education materials related to sexuality in pregnancy. No previously validated questionnaire was available for this specific purpose. Therefore, the questions were generated through an expert-driven conceptual process aimed at representing culturally prevalent and clinically relevant sexual myths. Each question was intentionally phrased in a manner similar to how patients might naturally seek information from an Artificial Intelligence–based system.

The simulation method was adopted as an ethically and methodologically accepted approach that allows for the evaluation of Artificial Intelligence–generated responses in the healthcare domain without the use of real user or patient data.[14-16] The aim was to examine the scientific accuracy, level of clarity, and appropriateness of ChatGPT's responses to such questions from the perspective of health communication.

Development of the Question Set

A total of ten questions were developed based on the most frequently reported myths and misconceptions regarding sexual activity during pregnancy as identified in the literature. These questions were grouped under the following thematic domains:

- fetal perception and consciousness,
- the possibility of physical or psychological harm to the fetus resulting from sexual intercourse,
- misconceptions linking sexual activity to fetal sex, intelligence, or personality development, and
- taboos rooted in religious or moral concerns.[1,2,6,8]

Each question was submitted to ChatGPT using a standardized user query format, and the responses generated by the system were recorded verbatim without modification.

RESULTS

In this study, responses generated by ChatGPT to ten simulated patient questions representing common but scientifically unfounded beliefs regarding sexual activity during pregnancy were analyzed. The responses were evaluated in terms of scientific accuracy, content consistency, communication style, and potential risk areas.

Examination of the thematic distribution of the simulated questions revealed that the content was grouped under four main categories (**Table 1**). These themes included misconceptions related to fetal perception and consciousness (such as the fetus being able to see, feel, or remember), safety concerns regarding the possibility of physical harm to the fetus resulting from sexual intercourse during pregnancy, misconceptions regarding developmental outcomes suggesting that sexual activity may have lasting effects on a child's intelligence, personality, or behavior, and concerns asserting that sexual intercourse is morally or religiously

inappropriate during pregnancy. The majority of these themes were found to be based primarily on cultural, emotional, or dogmatic beliefs rather than on physiologically grounded scientific concerns.

Table 1. Thematic classification of simulated questions related to sexual activity during pregnancy

Question no	Simulated question	Primary theme
Q1	Can the baby see us?	Fetal perception and awareness
Q2	Can the penis hit the baby's head?	Physical harm and safety concerns
Q3	Can the baby's psychology be harmed?	Developmental and psychological outcomes
Q4	Can sperm change gender?	Biological misconceptions
Q5	Will the baby be angry with us?	Emotional attribution to fetus
Q6	Can the baby suffocate?	Physical harm and safety concerns
Q7	Is sex a sin/does it harm the child's personality?	Moral and religious concerns
Q8	Will the baby talk early or become hyperactive?	Developmental outcome myths
Q9	Does external ejaculation make the baby smarter?	Developmental outcome myths
Q10	Can the baby feel pleasure?	Fetal perception and awareness

All questions were simulated to reflect commonly encountered nonscientific beliefs related to sexual activity during pregnancy.

Evaluation of the scientific accuracy of the responses generated by ChatGPT demonstrated that all responses were consistent with fundamental scientific principles related to pregnancy physiology and fetal development (**Table 2**). The responses particularly emphasized uterine anatomical structure, the protective function of the cervix, placental mediation of fetal oxygenation, and the limitations of fetal neurological development with respect to perception and consciousness. Responses addressing physical harm and safety-related concerns were observed to be clear and coherent in terms of anatomical and physiological explanations. In contrast, for questions containing moral or dogmatic elements, scientific explanations were presented using a more cautious and softened communication style.

Table 2. Scientific accuracy and content focus of ChatGPT responses

Thematic category	Core scientific explanation provided	Scientific accuracy
Fetal perception and awareness	Lack of visual, emotional, or sexual awareness; immature neurodevelopment	Accurate
Physical harm and safety concerns	Protection by uterus, amniotic fluid, and cervix; no direct contact	Accurate
Developmental outcome myths	No evidence linking sexual activity to intelligence, behavior, or personality	Accurate
Biological misconceptions	Sperm does not influence fetal gender after conception	Accurate
Moral and religious concerns	Focus on medical facts without moral judgment	Scientifically neutral

Scientific accuracy was evaluated based on consistency with established principles of obstetric anatomy and fetal physiology.

Analysis of the communication style and structure of the responses indicated that ChatGPT generally adopted an explanatory, calm, and non-directive tone (**Table 3**). In most responses, the use of medical terminology was limited, and complex concepts were explained using simple and accessible language. For questions attributing scientifically implausible characteristics to the fetus, such as perception, memory, or emotional awareness, an explanatory and normalizing approach was employed rather than a definitive or dismissive tone. In questions grounded in religious or moral concerns, direct value judgments were avoided, and the responses remained within the framework of medical information.

Table 3. Communication style and potential risk characteristics of ChatGPT responses

Evaluation domain	Observed characteristics
Language tone	Calm, explanatory, non-judgmental
Use of medical terminology	Limited and simplified
Handling of emotional or moral concerns	Neutral framing, avoidance of value judgment
Absolutist statements	Occasionally present
Mention of obstetric risk modifiers	Limited (e.g., placenta previa, preterm labor risk)
Potential user risk	Possible overgeneralization to individual clinical situations

The assessment reflects qualitative evaluation of response structure and language, not measured user outcomes

Assessment of potential risk areas revealed that although the responses were generally scientifically accurate, some statements exhibited an overly generalized nature. In particular, in several responses addressing the safety of sexual intercourse during pregnancy, conditions such as placenta previa, threatened preterm labor, or other obstetric risk factors were mentioned only to a limited extent. This was considered a potential limitation, as failure to adequately emphasize individual clinical circumstances may lead users to misinterpret their own situations.

Methodological Strengths and Limitations

Methodological strengths: This study has several methodological strengths that contribute to its conceptual and exploratory value. First, the study design explicitly acknowledges its simulation-based nature, avoiding any ambiguity regarding the origin of the data. By transparently defining the questions as simulated representations of commonly reported nonscientific beliefs, the study ensures ethical compliance and methodological clarity.

Second, the use of thematic analysis allowed for a structured examination of recurrent misconceptions related to sexual activity during pregnancy. Rather than focusing on isolated queries, the study contextualized these questions within broader sociocultural, moral, and educational frameworks, providing interpretive depth beyond simple content evaluation.

Third, the study integrates perspectives from obstetrics, reproductive health education, and digital health, enabling a

multidisciplinary interpretation of AI-generated responses. This approach aligns with emerging recommendations that emphasize the contextual evaluation of AI tools in healthcare communication rather than assessing factual accuracy alone.

Finally, the study contributes to the growing body of literature on artificial intelligence in medicine by highlighting how communication style and cultural sensitivity may influence the perceived adequacy of AI-generated health information. This conceptual emphasis represents a strength, as it shifts the focus from technological performance to patient-centered applicability.

Methodological limitations: Despite these strengths, several limitations must be acknowledged. This study did not analyze real patient-generated queries. Although the simulated questions were designed to reflect misconceptions frequently reported in the literature, they cannot fully capture the diversity, nuance, and emotional complexity of authentic patient interactions.

First, this analysis was limited to a single artificial intelligence–based large language model. As a result, the findings should be interpreted as system-specific and cannot be generalized to other AI platforms or model architectures. Comparative analyses involving multiple large language models may provide deeper insights into system-dependent and system-independent response patterns.

Second, the evaluation of the generated responses was primarily qualitative and exploratory in nature. While this approach allowed for in-depth thematic interpretation, future studies may benefit from incorporating quantitative indicators, such as the frequency of explicit safety warnings, references to obstetric risk modifiers, or the prevalence of absolute or overly generalized statements, to enhance methodological robustness.

Moreover, large language models are subject to continuous updates over time. The present study did not assess temporal consistency by repeating identical prompts at different time points.

Longitudinal evaluations of response stability may provide valuable information regarding the reliability of AI-generated health information.

The classification of hypothetical user characteristics such as educational level, cultural or religious sensitivity, and anxiety type was inferential rather than empirically verified. These categorizations were based on thematic interpretation rather than direct participant data, which may introduce subjective bias.

Third, the study did not include quantitative validation of response acceptance, such as real-time user feedback or behavioral outcomes. Therefore, conclusions regarding perceived adequacy of responses should be interpreted as conceptual observations rather than measurable effects.

Fourth, ChatGPT is a dynamic system that undergoes continuous updates. As a result, the responses analyzed in this study may not be reproducible in future versions of the model, limiting longitudinal generalizability.

Finally, while the study addresses ethical considerations related to data privacy and transparency, it does not evaluate the potential psychological impact of AI-generated responses on users. Future studies incorporating experimental or clinical validation would be necessary to assess real-world effectiveness and safety.

DISCUSSION

Why do These Questions Arise?

The emergence of such questions regarding sexual activity during pregnancy cannot be explained solely by a lack of knowledge. As highlighted in the literature, sexuality during pregnancy is strongly shaped by cultural norms, religious beliefs, moral values, and emotional projections.[2,3] In particular, beliefs that the fetus can perceive, remember, or be psychologically affected by sexual intercourse reflect symbolic and cultural thought patterns rather than biological reality.

Systematic reviews have shown that misconceptions about sexuality in pregnancy are widespread across different societies and are often fueled by fear, guilt, and moral concerns.[2] The study by Kaya et al.,[6] which compared different cultures, demonstrated that even when educational levels are similar, cultural and religious contexts play a decisive role in sustaining these myths. Moreover, studies examining the impact of pregnancy and childbirth on sexual behavior indicate that sexuality during this period is often perceived as "dangerous" or "inappropriate."[3]

In this context, the questions analyzed in our study should be considered not as "irrational" but as the result of socially learned belief systems transmitted across generations.

Why is Scientific Accuracy not Sufficient?

One of the key findings of this study is that scientifically accurate responses are not always accepted by users. In other words, scientific accuracy does not necessarily equate to acceptability. Particularly for questions with moral or dogmatic content, responses providing correct information were observed to have low levels of acceptance.

The literature indicates that while education level can influence the prevalence of sexual myths, it is not solely determinative.[2,6] Even highly educated individuals may reject information that conflicts with their cultural or religious values. This highlights that in health communication, merely "transmitting information" is insufficient; the way information is presented is at least as important as its content.

The language used in AI-based system responses plays a critical role in this context. Non-judgmental, normalizing, and explanatory language can reduce user resistance, whereas rigid or directly corrective statements may trigger defensive mechanisms. This represents an important communication lesson for healthcare professionals as well.

What does ChatGPT do Well, and What does It Not?

Analysis of the responses indicates that ChatGPT exhibits notable strengths, particularly regarding communication style. The system consistently used calm, non-judgmental, and normalizing language in most responses, providing

scientific explanations without dismissing user concerns. This approach aligns with previous studies emphasizing the empathetic aspects of AI responses.[13,14,16]

However, an important limitation of ChatGPT also emerged. While most responses emphasized that sexual activity during pregnancy is generally safe, limited attention was given to individual obstetric risk factors (such as placenta previa, threatened preterm labor, or history of bleeding). This suggests that generalized statements made outside the clinical context may create a false sense of security for some users.

Thus, ChatGPT's strengths are concentrated in communication and accessibility, whereas it remains insufficient in contexts requiring individualized clinical assessment.

Where is the Clinical Contribution?

One of the most important clinical contributions of this study is that such questions should not be dismissed as "trivial" or "irrational." On the contrary, these questions provide valuable insights into patients' knowledge levels, sources of anxiety, cultural background, and feelings of guilt.

Questions regarding sexuality during pregnancy can serve as an early warning system in patient–physician communication, even when not directly posed to a clinician. The literature shows that healthcare professionals often avoid providing counseling on these topics or do so inadequately.[11,18] When appropriately addressed, however, these questions can strengthen trust and enhance patient satisfaction.

In this context, patterns of questions obtained from AI systems can guide clinicians in shaping patient education and counseling strategies.

AI's Role: Tool or Authority?

The findings of this study clearly indicate that AI systems such as ChatGPT should be positioned as supportive tools rather than clinical authorities. AI can provide an anonymous, non-judgmental first point of contact for sensitive issues; however, it cannot replace clinical decision-making processes.

The World Health Organization and ethical literature emphasize that AI systems in healthcare should be transparent, limited in scope, and under human supervision.[15,17] The responses analyzed in this study suggest that AI can play an informative and educational role, but in areas requiring individual risk assessment and clinical responsibility, referral to healthcare professionals is essential.

In conclusion, AI-based systems can offer meaningful and safe contributions when viewed not as an authority replacing the clinician, but as a tool facilitating and supporting communication between patient and healthcare provider.

Limitations

Despite these limitations, this study provides a conceptual and descriptive framework for understanding how artificial intelligence systems may communicate sensitive health-related information during pregnancy, highlighting potential implications for patient education and digital health literacy. By illustrating both the strengths and potential risks of AI-generated responses to common sexual myths, these findings may inform clinicians, researchers, and developers in guiding the responsible integration of artificial intelligence into maternal health–related communication.

CONCLUSION

This study evaluated the content and communication characteristics of responses provided by ChatGPT to simulated patient questions representing common but scientifically unfounded beliefs about sexual activity during pregnancy. The findings indicate that this AI-based system employs calm, non-judgmental language consistent with fundamental obstetric and fetal physiology knowledge, and adopts a normalizing approach, particularly for questions involving cultural or moral concerns.

However, the limited emphasis on individual obstetric risk factors in the responses highlights a potential area of risk when used outside a clinical context. The results suggest that such questions should not be considered irrational, but rather viewed as the product of knowledge gaps, cultural transmission, and emotional projection.

When appropriately positioned, AI tools such as ChatGPT can contribute to clinical practice as supportive communication aids that help understand patient concerns. Nevertheless, it is essential to emphasize that these systems should be used as complementary tools in physician–patient communication, rather than as clinical decision-makers.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study did not require an ethics committee review because it used only publicly available and anonymized data extracted from ChatGPT interaction logs.

Informed Consent

This study did not require informed consent because it only used publicly available and anonymized data extracted from ChatGPT interaction logs.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The author declare no conflicts of interest related to this study.

Financial Disclosure

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Author Contributions

The design, data collection, analysis, and writing processes of the article were carried out by a single author.

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Review

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Elevated values in preeclampsia: diagnostic and prognostic role of NT-proBNP and ANP

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ABSTRACT

The aim of this review is to summarize the current understanding of the cardiac dimension of preeclampsia as reflected in the PubMed database, and to provide a perspective on how NT-proBNP and ANP may play a role in the future management of this challenging condition. This narrative review synthesizes evidence from observational and clinical studies in human pregnancies, indexed in PubMed, focusing on the diagnostic and prognostic roles of the cardiac biomarkers NT-proBNP and ANP in preeclampsia. NT-proBNP primarily serves as a marker of increased ventricular afterload, whereas ANP is more indicative of diastolic dysfunction and atrial stretch. The observation that both biomarkers are significantly elevated in patients with preeclampsia, correlate with disease severity, and have the potential to predict adverse maternal outcomes underscores their clinical relevance in this condition. Multiple studies have demonstrated that both NT-proBNP and ANP levels are significantly elevated in preeclamptic pregnancies compared with healthy normotensive controls.

Keywords: Preeclampsia, hypertension, brain natriuretic peptide, atrial natriuretic peptide

INTRODUCTION

Preeclampsia is a multisystem syndrome typically manifesting after the 20th week of gestation, characterized by hypertension (systolic ≥140 mmHg and/or diastolic ≥90 mmHg) and proteinuria (≥300 mg/24 hours or a protein/creatinine ratio ≥0.3), or by hypertension accompanied by multi-organ dysfunction involving the kidneys, liver, neurological system, or hematologic system.[1,2] It is one of the leading causes of maternal and perinatal morbidity and mortality, complicating approximately 3-8% of all pregnancies.[3] Its prevalence varies according to geographic region, socioeconomic factors, and maternal risk factors such as nulliparity, advanced maternal age, obesity, chronic hypertension, and diabetes.

The clinical significance of preeclampsia stems from the serious complications it can cause. Short-term maternal risks include eclampsia, HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome, placental abruption, acute kidney injury, pulmonary edema, and stroke. In the long term, affected women are at increased risk for chronic hypertension, cardiovascular disease, cerebrovascular events, and end-stage renal disease.[4] For the fetus and neonate, preeclampsia is associated with fetal growth restriction (FGR) due to uteroplacental insufficiency, fetal distress, preterm birth (iatrogenic or spontaneous), low birth weight, respiratory disorders such as respiratory distress syndrome, and even an elevated risk of intrauterine fetal death.[5]

The conventional criteria used for the diagnosis of preeclampsia have significant limitations. First, proteinuria does not consistently correlate with disease severity and may be minimal or even absent in some severe cases of preeclampsia.[2] Second, symptoms such as severe headache, visual disturbances, and upper abdominal pain, as well as organ dysfunction, typically manifest only after disease progression, limiting opportunities for early intervention. Third, the existing diagnostic criteria are inadequate for predicting the future course of the disease.

The pathogenesis of preeclampsia has not been fully elucidated. However, the most widely accepted model describes disease development in two stages: the first involves placental insufficiency, and the second is characterized by a maternal systemic response.[6]

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Placental stage (impaired spiral artery remodeling): This represents the first and clinically silent stage of the disease. In a normal pregnancy, trophoblast cells invade the uterine spiral arteries, remodeling their structure. This process transforms the vessels into wide, low-resistance conduits, ensuring adequate blood flow to the developing fetus.[7] In preeclampsia, however, this remodeling is inadequate. The spiral arteries remain narrow and retain their vasoconstrictive properties, resulting in placental ischemia and hypoxia.[8]

Maternal stage (systemic endothelial dysfunction): The hypoxic and ischemic placenta releases a range of factors into the maternal circulation. Among these, the imbalance between anti-angiogenic factors, such as soluble Fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng), and pro-angiogenic factors, including vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), plays a central role. sFlt-1 binds to VEGF and PlGF, rendering them inactive.[9] This imbalance, characterized by the predominance of anti-angiogenic factors, leads to widespread endothelial dysfunction in the maternal system.

Systemic Effects of Endothelial Dysfunction

The endothelium is the layer lining the interior of blood vessels and plays a vital role in maintaining vascular homeostasis. Endothelial dysfunction triggers the following processes, which contribute to the clinical manifestations of preeclampsia:

- **Increased systemic vascular resistance and hypertension:** In healthy endothelium, vasodilators such as nitric oxide are released to maintain vessel dilation. Endothelial injury disrupts this balance, enhancing the effects of vasoconstrictive agents such as endothelin-1. Consequently, the vessels constrict, systemic vascular resistance rises, and hypertension ensues.[10]

- **Increased vascular permeability and edema:** Disruption of endothelial integrity allows fluid and proteins to leak from the vasculature into surrounding tissues. This process contributes to edema and proteinuria, which are characteristic features of preeclampsia.

- **Multi-organ involvement:** Systemic endothelial dysfunction affects multiple organ systems.

  » Kidneys: Damage to glomerular endothelial cells leads to protein loss and renal dysfunction.

  » Liver: Endothelial injury in the liver contributes to elevated liver enzymes, right upper quadrant pain, and may predispose to HELLP syndrome.

  » Central nervous system: Cerebral edema, vasospasm, and microhemorrhages can result in severe headache, visual disturbances, hyperreflexia, and may ultimately progress to eclampsia.

  » Hematologic system: Endothelial injury triggers platelet activation and consumption, leading to thrombocytopenia.[11]

In summary, the process initiated by inadequate spiral artery remodeling progresses through placental release of anti-angiogenic factors, systemic endothelial dysfunction, and the resulting hypertension and multi-organ damage, culminating in the clinical presentation of preeclampsia. Impaired cardiovascular adaptive capacity and the consequent myocardial stress have emerged as increasingly recognized critical components in the complex pathogenesis of preeclampsia. In this context, N-terminal pro–brain natriuretic peptide (NT-proBNP) and atrial natriuretic peptide (ANP)-objective and reliable biomarkers of cardiomyocyte stress and hemodynamic load-warrant careful investigation for their potential clinical applications.

This review synthesizes evidence from human studies indexed in PubMed to examine the role of the cardiac biomarkers NT-proBNP and ANP in preeclampsia. We evaluate their contribution to pathogenesis, diagnostic accuracy, and prognostic prediction, aiming to clarify their potential for improving clinical management.

BIOLOGY AND PHYSIOLOGICAL ROLE OF NATRIURETIC PEPTIDES

ANP: Secretion and Effects

ANP is a hormone primarily synthesized and stored in the atria of the heart. The primary stimulus for ANP release is atrial stretch.[12] Atrial myocytes are stretched in response to increased blood volume and/or elevated venous return, which raises atrial pressure. Through this mechanical stimulus, ANP is rapidly secreted into the circulation.

The systemic effects of ANP are primarily directed toward reducing volume and pressure overload. These include natriuresis and diuresis: ANP relaxes the afferent arteriole and constricts the efferent arteriole in the renal glomeruli, thereby increasing the glomerular filtration rate (GFR). Additionally, it acts directly on the renal tubules to inhibit sodium (Na^+) and water reabsorption. As a result, urinary excretion of sodium and water is markedly increased, leading to a reduction in blood volume.[13]

Vasodilation: ANP acts on the smooth muscle cells of the vascular wall, promoting relaxation of the vessels. This leads to a reduction in systemic vascular resistance and blood pressure.

Inhibition of the renin–angiotensin–aldosterone system (RAAS): ANP directly suppresses renin release in the kidneys and aldosterone secretion from the adrenal glands, thereby counteracting the vasoconstrictive and fluid-retaining effects of the RAAS.[14]

Collectively, these effects of ANP play a key role in the regulation of body fluid and salt balance.

BNP and NT-proBNP: Secretion and Effects

BNP was first identified in brain tissue but is primarily secreted by the ventricles of the heart. Unlike ANP, it is not stored. Its synthesis and release are stimulated by increased wall tension and stress in ventricular myocytes.[15] Increases

in ventricular volume or pressure load, such as those seen in hypertension, are the main triggers for BNP production.

After secretion, BNP is divided into active BNP and inactive NT-proBNP. In clinical practice, measurement of NT-proBNP is generally preferred over BNP. The primary reasons for this preference are:

Longer half-life: The plasma half-life of NT-proBNP (60–120 minutes) is longer than that of active BNP (20 minutes). This allows NT-proBNP to remain at a more stable concentration in the circulation, making its measurement more reliable.[16]

Higher plasma concentration: Due to its longer half-life, NT-proBNP reaches higher circulating levels than BNP, facilitating laboratory measurement.

Greater stability: NT-proBNP is more stable at room temperature after sample collection, and its pre-analytical error rate is lower compared to BNP.

COMPARISON OF NT-proBNP AND ANP IN TERMS OF CLINICAL MEASUREMENT AND APPLICATION

Although both NT-proBNP and ANP are valuable biomarkers of cardiac stress, their applicability in clinical practice differs significantly. NT-proBNP is preferred and more suitable for routine use, particularly in cardiology and obstetrics clinics, due to its long half-life, high and stable plasma concentration, greater stability at room temperature, and the widespread availability of standardized commercial kits. In contrast, active ANP has a very short half-life, low basal plasma levels, and pre-analytical sensitivity requiring immediate cold-chain processing of the sample. Therefore, routine clinical measurement of ANP is more difficult and less practical compared to NT-proBNP. For this reason, ANP measurement is more commonly used in research settings, while NT-proBNP finds more use in daily practice for diagnosis, severity assessment, and prognostic prediction. However, the fact that ANP is particularly specific to atrial tension and diastolic dysfunction retains its value in terms of pathophysiological understanding.

NATRIURETIC PEPTIDE DYNAMICS IN NORMAL PREGNANCY

In a healthy pregnancy, the maternal circulatory system undergoes numerous important adaptive changes. Plasma volume increases by 40–50%, and cardiac output rises. These hemodynamic changes impose stress on the heart. Consequently, a mild elevation in natriuretic peptide levels in healthy pregnant women compared with non-pregnant women is considered physiological,[17] although this increase is generally modest.

In preeclampsia, however, the elevation in natriuretic peptides is typically much higher than the mild physiological increase observed in healthy pregnancies and is considered pathological. This excessive rise is driven by pathological afterload and cardiac dysfunction resulting from a marked increase in systemic vascular resistance. Therefore, by establishing appropriate threshold values, the pathological increase in preeclampsia can be readily distinguished from the physiological state of a healthy pregnancy.

PATHOPHYSIOLOGICAL BASIS OF CARDIAC STRESS IN PREECLAMPSIA

Hemodynamic Changes: Increased Afterload and Left Ventricular Loading

A central hemodynamic change in preeclampsia is a marked increase in systemic vascular resistance. This directly raises the afterload, defined as the pressure the left ventricle must overcome to eject blood into the aorta.[18] The elevated afterload places stress on the left ventricle, requiring it to exert greater effort with each contraction.

This increased workload has two major consequences:

- **Increased myocardial oxygen consumption:** As ventricular wall stress rises, the oxygen demand of the cardiac muscle increases.
- **Elevated left ventricular wall stress:** The mechanical stress (tension) on ventricular myocytes rises significantly as the ventricle works against high pressure to pump blood.

Increased afterload elevates left ventricular wall stress, which directly stimulates BNP synthesis and NT-proBNP release (**Figure**). Chronic pressure overload leads to left ventricular hypertrophy and diastolic dysfunction. Diastolic dysfunction increases left ventricular filling pressure, thereby raising left atrial pressure and tension. Increased atrial tension triggers ANP release. Consequently, the elevated NT-proBNP and ANP levels measured in preeclampsia are biochemical indicators of increased ventricular afterload/stress and diastolic dysfunction/atrial tension, respectively.

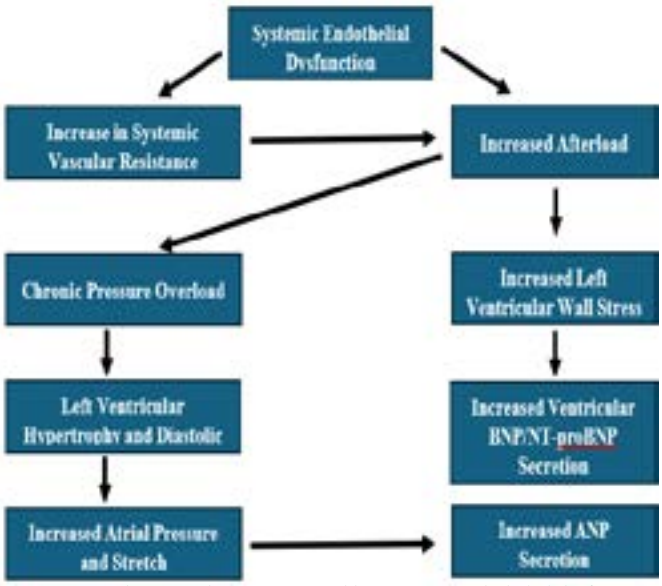

Figure. Hemodynamic changes triggered by systemic endothelial dysfunction in preeclampsia and the pathophysiological pathway of natriuretic peptide release
NT-proBNP: N-terminal pro–brain natriuretic peptide; ANP: atrial natriuretic peptide

Left Ventricular Hypertrophy and Diastolic Dysfunction

In response to increased afterload, the heart attempts to adapt over the long term. In preeclampsia, this process leads to concentric left ventricular hypertrophy, characterized

by thickening of the ventricular wall with a reduction or maintenance of the chamber volume.[19] Although this hypertrophy initially serves as a compensatory mechanism to counteract increased wall stress, it ultimately reflects a pathological process.

Myocardium that has undergone hypertrophy and exhibits increased oxygen demand is at risk for coronary microvascular dysfunction and ischemia. When these two factors—hypertrophy and ischemia-coexist, the left ventricle's ability to relax and fill is impaired, resulting in diastolic dysfunction.[20] Diastolic dysfunction means that higher pressures are required for ventricular filling. This elevated filling pressure is transmitted back to the left atrium, increasing atrial pressure and stretch, which in turn triggers ANP release[21] (**Figure**).

The elevation of both peptides indicates that preeclampsia is associated with impairments in both systolic and diastolic cardiac function.

Clinical Evaluation of NT-proBNP and ANP Levels in Preeclampsia

Numerous case-control studies have investigated this topic. Consistently, these studies have shown that both NT-proBNP and ANP levels are significantly higher in pregnant women with preeclampsia compared to healthy normotensive controls.

One of the pioneering studies on NT-proBNP, conducted by Resnik et al.,[17] reported markedly elevated BNP levels in women with preeclampsia compared to the control group. Similarly, in the study by Kale et al.,[22] NT-proBNP levels in the preeclampsia group (mean 430 pg/ml) were approximately six times higher than those in the control group (mean 74 pg/ml). Likewise, Suciu et al.,[23] in their systematic review and meta-analysis, reported significantly elevated NT-proBNP levels in the preeclamptic group, with the difference becoming more pronounced as disease severity increased.

A similar pattern is observed for ANP. Borghi et al.[24] demonstrated that ANP levels in preeclamptic women were significantly higher compared to both normotensive and chronically hypertensive pregnant women. This finding suggests that the cardiac stress observed in preeclampsia may have a dynamic profile distinct from that seen in chronic hypertension. Similarly, Pretorius et al.[25] reported markedly elevated ANP levels in the preeclampsia group compared to controls, with this increase correlating with disease severity. A comparative overview of these and other pivotal studies, including sample sizes, peptide levels, and diagnostic cut-offs, is provided in **Table**.

Correlation with Preeclampsia Severity

The clinical utility of NT-proBNP and ANP extends beyond diagnosis, as these biomarkers can also be used to assess disease severity. Studies have demonstrated that their

Table. Summary of key studies on NT-proBNP and ANP in preeclampsia

Study (year)	Study population	Sample size (n)	Measured peptide	Peptide levels (mean±SD or median)	Cut-off value (if applicable)	Sensitivity/ specificity	Key findings
Resnik et al. (2005)	Preeclamptic vs. normotensive pregnancies	Preeclampsia: 20, Control: 20	ANP	Preeclampsia: ↑↑, control: normal	Not specified	Not reported	BNP levels significantly higher in preeclampsia; correlates with disease severity.
Kale et al. (2005)	Preeclamptic vs. normotensive pregnancies	Preeclampsia: 30, Control: 30	NT-proBNP	Preeclampsia: ~430 pg/ml, control: ~74 pg/ml	Not specified	Not reported	NT-proBNP levels ~6x higher in preeclampsia group.
Suciu et al. (2025)	Systematic review & meta-analysis	Multiple studies included	NT-proBNP, BNP	Pooled analysis showed significant elevation	Not specified	Not reported	Confirmed significant elevation in preeclampsia, especially with severity.
Borghi et al. (2000)	Preeclamptic vs. normotensive & chronic hypertensive pregnancies	Preeclampsia: 15, normotensive: 15, chronic ht: 15	ANP	Preeclampsia: ↑↑, controls: lower	Not specified	Not reported	ANP levels higher in preeclampsia than in chronic hypertension.
Pretorius et al. (2018)	Preeclamptic vs. normotensive pregnancies	Preeclampsia: 40, control: 40	ANP	Preeclampsia: ↑↑, controls: normal	Not specified	Not reported	ANP levels correlate with disease severity.
Bakacak et al. (2016)	Severe vs. non-severe preeclampsia	Severe PE: 25, non-severe PE: 25	NT-proBNP	Severe PE: higher levels	Not specified	Not reported	NT-proBNP higher in severe preeclampsia; useful for severity grading.
Álvarez-Fernández et al. (2016)	Preeclamptic vs. normotensive pregnancies	Total: 120	NT-proBNP	Not specified	219 pg/ml	84%/76%	Good diagnostic accuracy; improves when combined with sFlt-1/PlGF.
Nan et al. (2025)	Preeclamptic vs. normotensive pregnancies	Total: 200	NT-proBNP	Not specified	116 pg/ml	90.9%/94.3%	High diagnostic accuracy for preeclampsia and maternal-fetal complications.
Reyna-Villasmil et al. (2018)	Preeclamptic vs. normotensive pregnancies	Total: 100	ANP	Not specified	0.66 ng/ml	87.8%/83.3%	Good diagnostic performance for ANP in preeclampsia.

SD: Standard deviation, ANP: Atrial natriuretic peptide, BNP: Brain natriuretic peptide, NT-proBNP: N-terminal pro–brain natriuretic peptide, HT: Hypertension, PE: Preeclampsia, sFlt-1: Soluble Fms-like tyrosine kinase-1, PlGF: Placental growth factor

concentrations are significantly higher in severe preeclampsia compared to mild cases.

In a study conducted by Bakacak et al.[26] in 2016, NT-proBNP levels were found to be higher in the severe preeclampsia group, suggesting that NT-proBNP could be used to grade the severity of preeclampsia. A similar pattern has been observed for ANP. In a study by Adam et al.,[27] serum ANP levels were reported to be significantly elevated in patients with severe preeclampsia and eclampsia.

These findings suggest that NT-proBNP and ANP can serve as measures of the pathophysiological impact of preeclampsia on cardiac load. As afterload and diastolic dysfunction worsen with disease progression, the serum levels of these peptides increase correspondingly. Therefore, these biomarkers are considered capable of reflecting the severity of preeclampsia in an objective and quantitative manner.

Diagnostic Accuracy and Threshold Values

Studies in the literature generally report high sensitivity and specificity for NT-proBNP in distinguishing preeclampsia from healthy pregnancies.

In a study by Álvarez-Fernández et al.,[28] using a cut-off value of 219 pg/ml, NT-proBNP demonstrated 84% sensitivity and 76% specificity for detecting preeclampsia, with even higher sensitivity and specificity when combined with sFlt-1/PlGF. A more recent study identified an optimal cut-off of 116 pg/ml, reporting a sensitivity of 90.9% and specificity of 94.3% for NT-proBNP alone.[29]

Reyna-Villasmil et al.,[30] in their study on the role of ANP in detecting preeclampsia, reported 87.8% sensitivity and 83.3% specificity at a cut-off value of 0.66 ng/ml.

There is no universally accepted threshold value for these peptides. Different studies have proposed varying cut-off ranges, with the main reasons for this variability being:

- Population differences: Variations in study populations, including gestational age, body-mass index (BMI), comorbidities, and race/ethnicity.
- Commercial kits and analyzers used: Differences in measurement standards across laboratories due to the use of various kits and analytical devices.
- Patient selection criteria: Heterogeneity in the severity distribution of preeclampsia cases included in the studies.

Due to these variations, establishing a universal reference range is challenging. Instead, it appears more appropriate for each laboratory to validate the biomarkers within its own population and using its specific methods, and to establish laboratory-specific reference ranges.

PROGNOSTIC ROLE OF NT-proBNP AND ANP

Prediction of Maternal Complications

The primary clinical potential of NT-proBNP and ANP lies less in diagnosis and more in their capacity to predict life-threatening maternal complications. Emerging studies suggest that elevated levels of these biomarkers may serve as indicators of a more severe disease course.

HELLP syndrome and eclampsia: In a study by Nan et al.,[29] patients who developed HELLP syndrome or required intensive care exhibited significantly higher baseline NT-proBNP levels compared to those with uncomplicated preeclampsia. Similarly, elevated ANP levels are thought to be associated with severe hypertensive crises and eclampsia. This is because these peptides indirectly reflect the severe hypertension and vascular dysfunction underlying cardiac decompensation and neurological involvement.

Pulmonary edema and cardiac complications: In preeclampsia, pulmonary edema typically arises as a consequence of diastolic dysfunction and increased capillary permeability. Both NT-proBNP (an indicator of diastolic dysfunction) and ANP (a marker of elevated atrial pressure) are directly linked to these pathophysiological processes. Therefore, elevated levels of these peptides may help identify patients at risk of developing pulmonary edema at an early stage.

Acute kidney injury: Reduced cardiac output and impaired renal perfusion can lead to kidney injury. As NT-proBNP is a sensitive marker of decreased cardiac output, it may have prognostic value in identifying the risk of preeclampsia-associated acute kidney injury.

Association with Fetal and Neonatal Outcomes

Maternal cardiovascular stress directly affects uteroplacental perfusion. Consequently, elevated maternal serum NT-proBNP and ANP levels are likely associated with fetal and neonatal complications.

FGR and preterm birth: Placental insufficiency is associated with both preeclampsia and FGR. Maternal hypertension and cardiac dysfunction further impair uteroplacental blood flow. Therefore, elevated NT-proBNP levels may serve as indicators of more severe placental dysfunction and, consequently, an increased risk of FGR and iatrogenic preterm birth.[30]

Low birth weight and fetal distress: Similarly, deterioration of maternal hemodynamics can contribute to the development of fetal distress. Several studies in the literature have reported associations between high maternal NT-proBNP levels and adverse neonatal outcomes, including low 5-minute Apgar scores, umbilical artery acidosis, and the need for neonatal intensive care unit admission.[29,30]

Monitoring Postpartum Cardiac Recovery

The adverse effects of preeclampsia on the maternal cardiovascular system do not resolve immediately after delivery. The postpartum period represents a recovery phase during which cardiac remodeling and hemodynamics gradually return to normal. NT-proBNP and ANP may serve as useful biomarkers for monitoring this process.

Limited studies have provided promising data in this regard. Research has shown that postpartum NT-proBNP levels in preeclamptic women decline rapidly, although this reduction may occur more slowly compared to normotensive women.[31] Persistently elevated NT-proBNP levels may indicate

incomplete cardiac recovery or permanent myocardial damage during the postpartum period.[32]

These findings support the potential utility of these cardiac biomarkers in assessing long-term cardiovascular risk in preeclampsia patients and in monitoring their postpartum recovery. However, further prospective studies are needed to establish postpartum-specific cut-off values and to delineate normal recovery dynamics.

DISCUSSION

The evidence presented in this review demonstrates that NT-proBNP and ANP serve as sensitive and objective biomarkers of cardiac stress and dysfunction, which play a central role in the pathophysiology of preeclampsia. NT-proBNP primarily reflects increased ventricular afterload, whereas ANP is more indicative of diastolic dysfunction and atrial stretch. Studies consistently report markedly elevated levels of both biomarkers in preeclamptic patients, their correlation with disease severity, and their potential to predict adverse maternal outcomes, highlighting their clinical value.

Routine use of these biomarkers in clinical practice could inform patient management in several ways:
Patient risk stratification: NT-proBNP, in particular, can be used to differentiate between "high-risk" and "low-risk" preeclampsia cases at the time of clinical presentation. Patients with elevated serum levels may warrant closer maternal monitoring (e.g., frequent blood pressure checks, laboratory assessments) and enhanced fetal surveillance (e.g., non-stress tests and ultrasonography). These biomarkers may even help anticipate the need for hospitalization.

Individualization of follow-up protocols: Serial measurements of these biomarkers can provide an objective assessment of preeclampsia progression or stabilization. Declining or stable levels may be interpreted as reassuring, whereas rising levels could prompt reconsideration of the therapeutic strategy.

CONTRADICTIONS AND METHODOLOGICAL DIFFICULTIES

In the literature, there is a general consensus regarding the diagnostic performance of NT-proBNP and ANP in preeclampsia. Nevertheless, inconsistencies remain among studies concerning the proposed cutoff values and certain prognostic associations. These discrepancies are largely attributable to methodological differences and the influence of confounding factors.

These include:
Gestational age: NT-proBNP and ANP levels may vary across different trimesters of pregnancy. Since the populations examined in various studies often include patients at different gestational stages, this heterogeneity can distort the results.

Preexisting cardiovascular and metabolic disorders: Conditions such as obesity, chronic hypertension, diabetes, or preexisting cardiac disease may independently influence these peptide levels; therefore, the observed elevations may not be specific to preeclampsia alone.

Population heterogeneity: Differences in ethnicity, age, and BMI distributions among study populations can affect the generalizability of findings.

Analytical variability: The lack of standardization among commercially available assay kits and measurement platforms makes it difficult to compare cutoff values across studies.

Clinical practice applicability and marker selection: While evidence in the literature suggests that both NT-proBNP and ANP reflect cardiac stress in preeclampsia, NT-proBNP has a clear advantage when it comes to translating these markers into clinical practice. Technical challenges in measuring ANP and the limited availability of standardized, widely accepted test kits make its integration into routine diagnostic or prognostic algorithms difficult. In contrast, automated, rapid, and reliable measurement systems have been developed for NT-proBNP, and its use in clinical laboratories is becoming increasingly common. This practical advantage increases the potential for NT-proBNP to be considered as a first-line biomarker in the management of preeclampsia. ANP, on the other hand, may play a more central role in mechanistic studies or as a complementary marker that can further clarify the pathophysiological picture when used in conjunction with NT-proBNP.

Lack of detailed subgroup analyses: The current literature and the scope of this review do not include detailed subgroup analyses of key confounding factors that may have significant effects on NT-proBNP and ANP levels. Specifically:

- **Gestational age:** Understanding how NT-proBNP and ANP levels vary across trimesters and even specific weeks of pregnancy is critical for establishing gestational week-specific reference ranges for these markers. Current studies often analyze heterogeneous groups of patients at different gestational weeks, making interpretation of results challenging.

- **BMI:** Obesity is thought to independently influence natriuretic peptide levels due to its known effects on cardiac structure and function. However, comprehensive analyses comparing the behavior of these markers in obese and normal BMI pregnant women with preeclampsia are limited.

- **Pre-existing cardiovascular and metabolic diseases:** Conditions such as chronic hypertension, diabetes, or subclinical heart disease can elevate natriuretic peptide levels independently of pregnancy. To differentiate the preeclampsia-specific increase from the increase caused by these underlying conditions, controlled subgroup analyses are needed in preeclampsia groups with and without these comorbidities.

In studies where these confounding factors are not systematically controlled for or isolated, it is difficult to determine the extent to which measured natriuretic peptide elevation is specific to preeclampsia and to what extent it is due to these other factors. This leads to uncertainty both in determining diagnostic thresholds and in prognostic interpretation.

Future research directions: The methodological challenges and shortcomings highlighted above underscore the need for further research in the following areas:

- **Large-scale, prospective, multicenter cohort studies:** Well-designed, multicenter cohort studies involving diverse populations are needed to establish gestational age–specific reference ranges for NT-proBNP and ANP, and to validate their diagnostic and prognostic accuracy after adjustment for confounding factors.

Multi-Marker Approaches

Rather than relying on a single biomarker, panels that reflect different pathophysiological pathways may offer greater clinical insight. For instance, combining markers of cardiac stress (NT-proBNP/ANP) with those of placental dysfunction (sFlt-1/PlGF ratio) could substantially improve both diagnostic precision and prognostic performance compared to using each marker in isolation.

Despite the theoretical advantages of the multi-marker approach, its integration into routine clinical practice should also be evaluated in terms of cost-effectiveness, test accessibility, and workflow. Measurement of angiogenic markers such as the sFlt-1/PlGF ratio can often be more expensive than NT-proBNP and may not be routinely used in all centers, especially those with limited resources. NT-proBNP, on the other hand, is an automated and relatively low-cost test already available in many hospitals due to its widespread use in the diagnosis and monitoring of heart failure. Therefore, NT-proBNP alone can be a valuable screening or risk stratification tool, especially in settings where the sFlt-1/PlGF test is not routine. In an ideal scenario, combining markers from both pathways (placental and cardiac) would provide the highest diagnostic and prognostic accuracy. However, it is thought that the cost-benefit ratio of this combination can only be justified in high-risk pregnancy centers or in cases of significant clinical suspicion. Widespread adoption of this approach as a routine measure will depend on lower testing costs, standardization, and robust evidence demonstrating that these panels improve clinical outcomes.

Interventional studies: The highest level of evidence required for the clinical implementation of these biomarkers will come from randomized controlled trials. Future studies could investigate whether biomarker-guided risk stratification-such as more intensive management or closer monitoring of patients with elevated NT-proBNP and ANP levels-can effectively reduce maternal and neonatal morbidity.

CONCLUSION

As a result, evidence indicates that both NT-proBNP and ANP levels are significantly elevated in women with preeclampsia compared to healthy normotensive pregnancies. This elevation is directly and causally linked to the hemodynamic alterations characteristic of preeclampsia, including increased systemic vascular resistance, elevated left ventricular afterload, and the resulting diastolic dysfunction-all reflecting heightened cardiac stress and dysfunction. NT-proBNP and ANP thus emerge as promising biomarkers for understanding and managing the cardiac dimension of preeclampsia.

However, for their integration into routine clinical practice, several prerequisites remain essential: the standardization of measurement methodologies, the establishment of gestational age–specific cutoff values through large-scale prospective studies, and stronger evidence derived from multi-marker and interventional trials. Conducting such studies will substantially contribute to reducing the maternal and fetal complications associated with preeclampsia.

ETHICAL DECLARATIONS

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This review was externally peer-reviewed.

Conflict of Interest

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Intramuscular hemangioma in the foot of a child: a rare case report

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ABSTRACT

Intramuscular hemangiomas are rare benign vascular tumors. Plantar foot involvement is exceptionally uncommon and poses unique diagnostic and therapeutic challenges due to the weight-bearing nature of the region. We report the case of a 10-year-old girl who presented with a slowly progressive, painful mass in the medial plantar region of the left foot. Physical examination revealed a deep-seated, mildly tender nodular lesion without overlying skin changes or functional limitation. Magnetic resonance imaging demonstrated a well-circumscribed lesion located within the flexor digitorum brevis muscle, showing signal characteristics consistent with an intramuscular hemangioma. Based on the benign radiological features, limited lesion size, absence of functional impairment, and potential risks associated with surgical or interventional treatment, a conservative management strategy with close clinical follow-up was adopted. Intramuscular hemangiomas may remain clinically silent for years and become symptomatic with growth, mechanical loading, or increased physical activity. Treatment options include surgery, sclerotherapy, and observation; however, in selected pediatric cases, conservative follow-up may be preferable to avoid unnecessary morbidity. When clinical and imaging findings indicate benign behavior and lesion stability, structured conservative follow-up represents a safe and effective management approach.

Keywords: Intramuscular hemangioma, pediatric soft tissue tumor, plantar foot, case report

INTRODUCTION

Intramuscular hemangiomas (IMHs) are rare vascular tumors of benign nature that arise within skeletal muscle tissue and may pose significant diagnostic challenges both clinically and radiologically. They are reported to account for less than 1% of all hemangiomas. Although most cases occur during childhood and young adulthood, diagnosis is frequently delayed, and lesions may be followed for prolonged periods with incorrect preliminary diagnoses such as soft tissue masses, muscle strain, or sequelae of trauma. In particular, some infantile lesions—especially superficial infantile capillary hemangiomas—may regress spontaneously and require only observation.[1]

The etiopathogenesis of IMHs has not been fully elucidated. They are largely considered to be of congenital origin, arising from vascular developmental anomalies during the embryonic period. The hemodynamic and molecular genetic phenotypes closely resemble those observed in angiovenous malformatioons. Newly identified mutations, including cases with coexisting mutation types, and insertion mutations offer valuable insights into the genetic basis of vascular anomalies.[3] However, cases that are not clinically apparent at birth and become symptomatic during childhood or adolescence have also been reported. This phenomenon is thought to be related to the ability of these lesions to remain quiescent for long periods and to become clinically evident with growth or increased physical activity.

From an anatomical perspective, IMHs are most commonly located in the lower extremities, particularly within the thigh and calf muscles. In contrast, involvement of the foot and plantar region is exceedingly rare. The plantar surface of the foot is subjected to substantial mechanical load and has a complex anatomical structure, and because surgical interventions in this region carry a high risk of functional impairment, IMHs in this location require special consideration during clinical decision-making.

Magnetic resonance imaging (MRI) is regarded as the gold standard for the diagnostic evaluation and characterization of IMHs.[2] On T1-weighted sequences, these lesions typically appear iso- to mildly hypointense and may demonstrate a heterogeneous structure containing foci of high signal intensity corresponding to intralesional fat; on T2-weighted images, marked hyperintensity is characteristic.[4] These radiological features support the benign vascular nature of the

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lesion and facilitate differentiation from lipoma, fibromatosis, rhabdomyosarcoma, and other soft tissue tumors.

Treatment options include surgical excision, sclerotherapy, embolization, and conservative observation. Particularly in pediatric patients, an individualized treatment strategy should be adopted, taking into account lesion location, symptom severity, growth rate, and functional impact. In this case report, we discuss the clinical course and conservative management of a 10-year-old girl diagnosed with a symptomatic intramuscular hemangioma of the plantar foot that did not result in functional impairment, in the context of the relevant literature.

CASE

A 10-year-old girl presented to our outpatient clinic with complaints of a palpable mass in the plantar surface of the left foot that had been noticed for several years, accompanied by pain during walking. There was no history of significant trauma, infection, or previous surgical intervention. The patient's family reported that the mass was initially very small but had become more apparent in recent years, with pain increasing particularly after prolonged walking or physical activity. There was no history of nocturnal pain, rest pain, or systemic symptoms.

Physical examination revealed a deep-seated, nodular lesion approximately the size of a hazelnut in the medial aspect of the plantar surface of the left foot, causing mild tenderness on palpation. The overlying skin appeared normal, with no discoloration, increased temperature, or superficial vascular prominence. Range of motion of the foot and ankle joints was full and painless. Neurological examination revealed no sensory deficits or reflex abnormalities. Peripheral pulses were palpable and normal.

Plain radiographs of the foot obtained for initial evaluation were unremarkable, showing no evidence of bone destruction, periosteal reaction, or calcification. Subsequently, MRI was performed. Imaging demonstrated a well-circumscribed mass measuring approximately 20×15×20 mm within the flexor digitorum brevis muscle, with smooth margins and no infiltrative characteristics. On T1-weighted images, the lesion exhibited intermediate signal intensity, with small high-signal foci around the lesion suggestive of fatty deposits (**Figure**). On T2-weighted sequences, the lesion showed marked hyperintensity compared with the surrounding skeletal muscle. Contrast-enhanced imaging revealed heterogeneous enhancement. These radiological findings were consistent with the diagnosis of an intramuscular hemangioma.

The patient's clinical and radiological findings were evaluated in a multidisciplinary setting. Considering the limited size of the lesion, the absence of infiltrative features, the lack of significant functional impairment, and the young age of the patient, invasive treatment options such as surgical excision or sclerotherapy were not pursued. The benign nature of the lesion, its potential natural course, and the circumstances that might necessitate intervention were explained in detail to the patient and her family. Regular clinical and radiological follow-up was recommended.

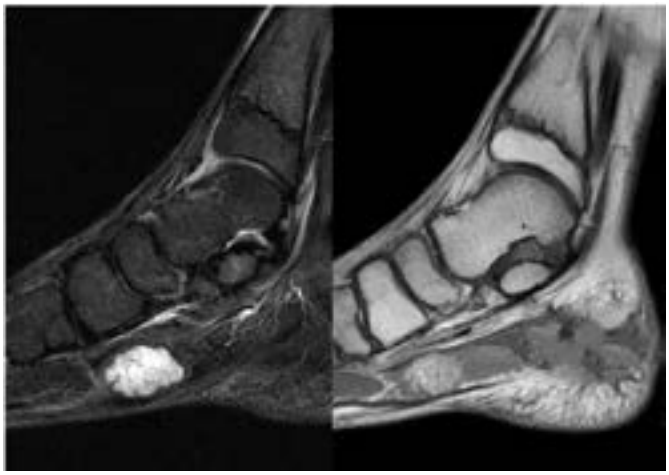

Figure. Intramuscular hemangioma

During follow-up, the patient continued to experience intermittent pain; however, this did not reach a level that restricted daily activities or school life. No clinically significant increase in lesion size was observed. Given that musculoskeletal development would continue through adolescence and young adulthood, conservative management was maintained until completion of growth.

DISCUSSION

Hemangiomas are among the most common benign soft tissue tumors of infancy and early childhood and show a marked female predominance in the general population.[5] The male-to-female ratio has been reported to range between 1:3 and 1:5 in the literature.[6] Regarding anatomical distribution, approximately 60% of cases occur in the head and neck region, 25% in the trunk, and 15% in the extremities. Within this distribution, intramuscular localization is particularly rare, accounting for less than 1% of all hemangiomas.

Classically, congenital hemangiomas are present within the first month of life and progress through three phases: proliferative, stable, and involutional. With an incidence of 4–10%, infantile hemangiomas (IH) are the most encountered benign tumors in infancy.[1,2] They are characterized by a phase of rapid growth, followed by a progressive involution.[5] The proliferative phase is usually most prominent during the first 6–12 months, followed by a gradual regression over subsequent years. Most superficial lesions, commonly referred to as "strawberry hemangiomas," undergo spontaneous involution between 18 months and 10 years of age.[7] However, hemangiomas located intramuscularly or beneath the deep fascial layers may not follow this typical course; they can remain clinically silent for prolonged periods and become symptomatic during late childhood or adolescence.

One of the rare features of the present case is the localization of the lesion in the plantar region of the foot, which is an uncommon anatomical site. IMHs of the lower extremity are most frequently reported in the thigh and calf muscles, whereas plantar involvement—particularly within the flexor digitorum brevis muscle—has been described only in a limited number of cases. As a weight-bearing area, the plantar surface of the foot may become painful even with small-volume lesions, although functional impairment does not

necessarily accompany the pain. Such lesions may be difficult to detect while the patient is at rest, as the hemangioma may not be engorged with blood. However, asking the patient to stand for 3–4 minutes may help reproduce typical symptoms.[8] Similarly, in the present case, the patient reported pain during walking and physical activity, but no functional limitation affecting daily activities was observed.

Another distinctive aspect of this case is that the lesion was not recognized during the congenital period and became clinically apparent only over the past few years. This observation suggests that IMHs are not always diagnosed in early childhood and may become symptomatic in association with mechanical loading, growth, and increased physical activity. This variability highlights the heterogeneous biological behavior of hemangiomas and indicates that a uniform clinical course cannot be assumed.

From a differential diagnostic perspective, a wide range of infectious, inflammatory, and neoplastic conditions should be considered in pediatric patients presenting with a painful plantar mass. Deep-seated abscesses, in particular, may present with pain and tenderness; however, they are typically associated with acute onset, erythema, increased local temperature, systemic signs of infection, and elevated inflammatory markers. On MRI, abscesses are characterized by central fluid signal intensity and prominent peripheral contrast enhancement. The absence of these clinical and radiological features in the present case strongly excluded an infectious process. Other conditions such as plantar fibromatosis, lipoma, nerve sheath tumors, and malignant soft tissue tumors were also considered, but MRI findings were most consistent with an intramuscular hemangioma.

Although hemodynamic complications are rare in IMHs, deep and large-volume lesions have been associated with thrombosis, local hematoma formation, and, rarely, circulatory overload related to high-flow vascular anomalies. Several vascular tumors and malformations are associated with complex coagulation derangements.[9] In small, low-flow lesions confined to limited anatomical regions such as the plantar foot, the likelihood of such complications is extremely low. This consideration further supported the decision for conservative management in the present case.

Among treatment options, sclerotherapy is often preferred for diffuse lesions or those unsuitable for surgical excision due to the risk of functional impairment. Commonly used sclerosant agents include ethanol, polidocanol, sodium tetradecyl sulfate, and bleomycin, which induce endothelial damage leading to fibrosis and lesion shrinkage. However, in pediatric patients—particularly in sensitive regions such as the plantar foot—sclerotherapy carries risks including skin necrosis, nerve injury, muscle fibrosis, and long-term functional impairment. Therefore, indications for sclerotherapy should be carefully evaluated.

Surgical excision is generally reserved for cases with severe pain, rapid growth, functional impairment, neurovascular compression, or significant cosmetic concerns. Nevertheless, complete resection of IMHs is not always feasible, and high postoperative recurrence rates have been reported. Parents are often advised to avoid early surgical intervention, as approximately 50% of these hemangiomas regress by the age of 5 years and up to 70% by the age of 7 years.[10] In addition, plantar foot surgery carries inherent risks such as scar formation, altered load distribution, and chronic pain. Surgical management of hemangiomas is further complicated by their vascular nature, infiltrative growth within muscle tissue, and high recurrence rates.[11]

Long-term follow-up is therefore recommended for these lesions. Tang et al.,[12] in a study predominantly involving adult patients, reported that most recurrences occurred within 2 years, although some were observed as late as 6 years after primary surgery. They also noted that 50% of patients with recurrent disease required additional surgical intervention.

In the present case, choosing not to intervene carried certain theoretical risks, including potential lesion growth, increased pain severity, or rare local complications. However, given the current clinical presentation, these risks were considered low, whereas the potential complications associated with early surgical or interventional treatment were deemed more significant. Accordingly, the patient was managed with close clinical follow-up and a symptom-oriented conservative approach.

CONCLUSION

IMHs of the plantar foot are exceedingly rare and should be considered in the differential diagnosis of painful, late-presenting soft tissue masses in pediatric patients. In selected cases where clinical and MRI findings indicate benign behavior, lesion stability, and absence of functional impairment, close and structured conservative follow-up may represent a safe and effective management strategy, avoiding unnecessary morbidity associated with early surgical or interventional treatments.

ETHICAL DECLARATIONS

Informed Consent

Informed consent was obtained from the legal guardians of the pediatric patient(s) described in this report. Where developmentally appropriate, assent was also sought from the child. The inclusion of vulnerable populations in this study adhered to national and international ethical guidelines. Extra care was taken to ensure voluntary participation, understanding, and protection of participant dignity and autonomy.

Peer Review Process

This report underwent external peer review.

Conflict of Interest

The authors declare no conflicts of interest.

Financial Disclosure

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Author Contributions

The design, data collection, analysis, and writing processes of the article were carried out by a single author.

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Mehmet Kabalcı

I was born in Kahramanmaraş. In 2002, I graduated from Istanbul University Faculty of Medicine and embarked on my career as a doctor, a profession I had dreamed of since childhood and dearly loved. In 2011, I completed my training at İstanbul Bilim University Florence Nightingale Hospital and became a specialist in cardiovascular surgery. I started working at Kırıkkale University Faculty of Medicine as an Assistant Professor in 2013 and continue to work there as an Associate Professor. I have conducted research in the biomedical field and developed patents. We established Implanox at Kırıkkale University Technopark, where we develop surgical and orthopaedic products, taking this work to a more professional level. My hobbies include nature walks, motocross, and travelling to unexplored places.

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Case Report

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Laparoscopic management of adnexal torsion during pregnancy

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ABSTRACT

Acute pelvic pain during pregnancy presents a diagnostic challenge because of its broad differential diagnosis and pregnancy-specific considerations. Adnexal torsion is an uncommon but clinically significant gynecological emergency, and its occurrence during the second trimester is particularly rare. Delayed diagnosis may result in irreversible ischemic damage, loss of ovarian function, and potential adverse maternal–fetal outcomes. We report the clinical course and laparoscopic management of adnexal torsion in an 18-week pregnant patient presenting with acute abdomen. Diagnostic laparoscopy revealed right adnexal torsion with five complete twists around the vascular pedicle. Laparoscopic detorsion was successfully performed, followed by adnexal fixation to the right lateral abdominal wall to reduce the risk of recurrence. Restoration of ovarian perfusion was observed intraoperatively. No maternal or fetal complications occurred during the postoperative follow-up. This case highlights the feasibility and safety of a fertility-preserving laparoscopic approach for adnexal torsion during the second trimester of pregnancy.

Keywords: Adnexal torsion, pregnancy, second trimester, acute pelvic pain, laparoscopy

INTRODUCTION

Adnexal torsion (AT) is a gynecological emergency characterized by partial or complete rotation of the ovary and/or fallopian tube around its vascular pedicle, leading to impaired venous and arterial blood flow.[1] Timely diagnosis and surgical intervention with restoration of the adnexa to their anatomical position are essential to prevent irreversible ischemic injury and loss of ovarian function.[2]

The majority of AT cases occur in women of reproductive age. Pregnancy is considered a significant risk factor for the development of AT due to hormonal and anatomical changes. It has been reported that 8–28% of torsion cases occur during pregnancy, most commonly in the first trimester; however, AT may be diagnosed at any gestational age.[3,4] The reported incidence of AT during pregnancy ranges from 3 to 5 cases per 10,000 pregnancies, although this figure varies across populations and study designs.[5]

Despite advances in imaging, the diagnosis of AT during pregnancy remains challenging, particularly beyond the first trimester, because physiological and anatomical changes may obscure classical clinical and radiological findings. Furthermore, acute pelvic pain in pregnant patients requires exclusion of obstetric conditions such as miscarriage, placental abruption, or uterine rupture. This case report addresses the clinical gap related to the diagnosis and laparoscopic management of AT during the second trimester of pregnancy, a relatively rare but high-risk clinical scenario.

CASE

A 30-year-old patient, gravida 2, para 0, living 0, abortus 1 (G2P0L0A1), presented at 18 weeks of gestation according to her last menstrual period with progressively worsening right-sided groin pain that began in the morning hours. The pain was accompanied by nausea and vomiting. The patient had no known history of ovarian cysts, adnexal masses, prior pelvic surgery, or assisted reproductive treatment.

On physical examination, marked abdominal tenderness with guarding and rebound was noted. Obstetric ultrasonography revealed a single, viable fetus in cephalic presentation, with biometric measurements consistent with gestational age. The placenta was located anteriorly, and no evidence of placental abruption or retroplacental hematoma was observed. There was no vaginal bleeding. Transvaginal examination demonstrated cervical motion tenderness and significant pain in the pouch of Douglas.

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Abdominal ultrasonography showed an enlarged right ovary with reduced blood flow on Doppler evaluation. Based on the clinical and radiological findings, AT was suspected, and emergency surgical intervention was planned.

Fetal monitoring was conducted preoperatively and postoperatively. Laparoscopy was performed with trocar placement adapted to the enlarged uterus. We started with the insertion of a Veress needle into the peritoneal cavity, after a little incision of the above 2 cm umbilicus. The needle is pushed in until it gives a double click, ensuring that it is in the intraperitoneal space. Once into peritoneal cavity, gas insufflation is provided. Pneumoperitoneum was established using carbon dioxide at an intra-abdominal pressure of 10–12 mmHg. A three-port laparoscopy was performed, with the primary 10-mm port being inserted through the above 2 cm umbilicus for the 10-mm telescope. Two additional 5 mm ports were placed to the left and right of the original trocar at the same level of the abdomen. Laparoscopic exploration revealed that the right adnexa was twisted five complete turns around its vascular pedicle (**Figure 1**). Laparoscopic detorsion was performed (**Figure 2**), followed by fixation of the adnexa to the right lateral abdominal wall using absorbable 1.0 sutures to reduce the risk of recurrence and fertility (**Figure 3**). Restoration of ovarian perfusion was observed shortly after detorsion. Operation duration was 35 minutes. After the operation, we did ultrasound and check the baby's heart rate.

Postoperatively, the patient experienced complete resolution of pain. Preoperative laboratory investigations revealed a white blood cell count of 18,000/mm³ and a C-reactive protein (CRP) level of 28 mg/L,3 which decreased to 9,000/mm³ and 8 mg/L, respectively, on postoperative day one. The patient tolerated oral intake after the passage of flatus and stool and was discharged uneventfully on postoperative day one.

Figure 1. Laparoscopic view demonstrating right adnexal torsion with multiple twists around the vascular pedicle

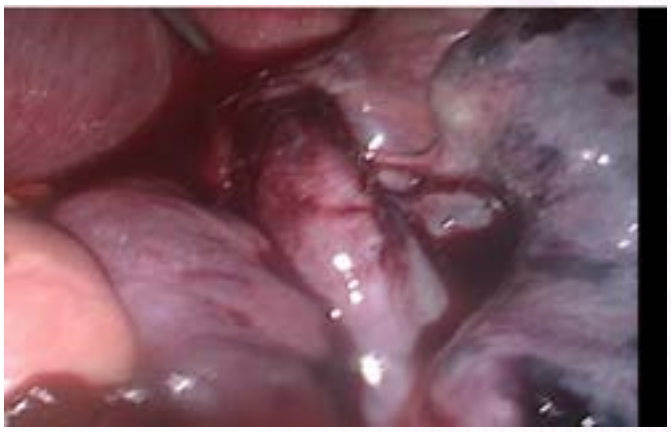

Figure 2. Laparoscopic detorsion of the right adnexa with visible improvement in tissue color

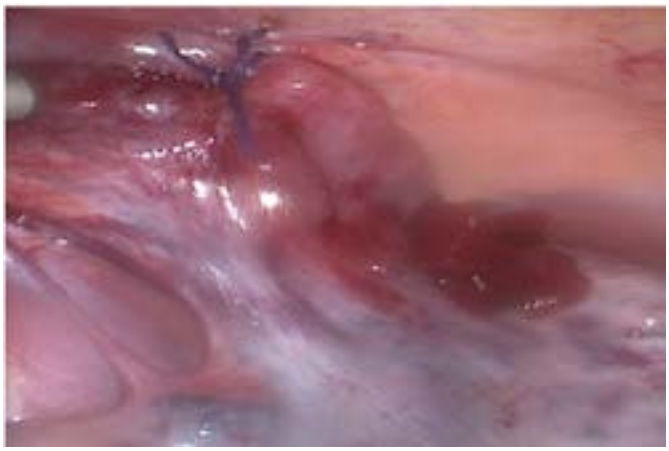

Figure 3. Fixation of the right adnexa to the lateral abdominal wall to reduce the risk of recurrence

DISCUSSION

AT during pregnancy is an uncommon but potentially serious surgical emergency with implications for both maternal and fetal outcomes. Although most cases are diagnosed during the first trimester, torsion can occur at any gestational age, including the second trimester, as demonstrated in the present case.[3,4] Its reported incidence ranges from 3 to 5 cases per 10,000 pregnancies.[5]

AT most commonly occurs in the presence of an underlying ovarian pathology. The most frequently reported risk factors include ovarian cysts, prior pelvic surgery, and assisted reproductive technologies. However, as demonstrated in the present case, torsion may also occur in a normal ovary. Diagnosis during pregnancy is particularly challenging due to anatomical changes caused by uterine enlargement and the need to exclude pregnancy-specific differential diagnoses such as miscarriage, retroplacental hematoma, or uterine rupture.

The clinical presentation typically consists of sudden-onset, severe lower abdominal pain, often accompanied by nausea, vomiting, and low-grade fever. Ultrasonography is the first-line imaging modality for suspected AT. Findings such as ovarian enlargement, stromal edema, peripherally displaced follicles, and reduced or absent blood flow may support the diagnosis. Although absent Doppler flow strengthens the suspicion of torsion, normal Doppler findings do not exclude the diagnosis. Magnetic resonance imaging may serve as a useful adjunct when ultrasonography is inconclusive; however, it should not delay surgical intervention.[6]

Surgical management is the standard of care for AT. Current evidence supports the safety of laparoscopy during pregnancy when appropriate precautions are taken, including modified trocar placement and low pneumoperitoneum pressures.[7,8]

Conservative surgery with detorsion is recommended whenever viable adnexal tissue is present, as ovarian function

can be preserved in up to 90% of cases following detorsion. The choice between conservative and radical surgery depends on the viability of the adnexa following detorsion. In the presence of viable tissue, conservative management with detorsion is recommended to preserve ovarian function. Previous studies have reported recovery of ovarian function in approximately 90% of cases following detorsion. Adnexal fixation should be considered in cases with a high risk of recurrence.[9]

Adnexal fixation after detorsion remains controversial. In the literature, various surgical strategies have been described to prevent recurrence after detorsion. Particularly during pregnancy, several authors have favored tubal shortening over adnexal fixation, based on the assumption that reducing tubal length and mobility may decrease the risk of recurrent torsion. For this reason, tubal shortening has been reported as a preferred approach in many studies.[10,11] In the present case, adnexal fixation was performed in consideration of the degree of torsion and the potential risk of recurrence during pregnancy, with the aim of preserving fertility and minimizing future complications.[10,11]

The patient's pregnancy continued without complication following surgery. Although long-term obstetric outcomes were favorable in this case, including continuation of pregnancy, further data are needed to clarify optimal management strategies and long-term maternal and neonatal outcomes in cases of AT during pregnancy.

CONCLUSION

The diagnosis of AT during pregnancy is challenging because of nonspecific clinical and radiological findings, particularly in the second trimester. Prompt surgical intervention and a conservative laparoscopic approach, including detorsion with or without adnexal fixation, are essential to preserve ovarian function and ensure favorable maternal and fetal outcomes.

ETHICAL DECLARATIONS

Informed Consent

For pregnant patient, written informed consent was obtained with a full explanation of maternal and fetal implications. Signed consent forms are on file and available upon request. The inclusion of vulnerable populations in this study adhered to national and international ethical guidelines. Extra care was taken to ensure voluntary participation, understanding, and protection of participant dignity and autonomy.

Peer Review Process

This report underwent external peer review.

Conflict of Interest

The authors declare no conflicts of interest.

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Author Contributions

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Case Report

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Complement-mediated warm autoimmune hemolytic anemia associated with acute poststreptococcal glomerulonephritis: a pediatric case report

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ABSTRACT

Acute poststreptococcal glomerulonephritis (APSGN) is one of the most common causes of acute nephritic syndrome in childhood; however, hematological complications are rarely associated with this disease. This article presents a case of a 6.5-year-old male who presented with complaints of pallor and fatigue after a recent upper respiratory tract infection and was diagnosed with autoimmune hemolytic anemia. During hospitalization, the patient developed hypertension, oliguria, and gross hematuria; further evaluation revealed elevated antistreptolysin O levels and markedly low serum complement component 3 levels, leading to a diagnosis of APSGN. The direct antiglobulin test revealed immunoglobulin G negativity along with complement positivity, findings consistent with complement-mediated warm-type autoimmune hemolytic anemia. The patient received corticosteroid therapy, supportive treatment, and antihypertensive agents; following treatment, rapid improvement in hemoglobin levels and complete resolution of renal and hematological findings were achieved. This case highlights the rare association of APSGN with complement-mediated autoimmune hemolytic anemia, emphasizing the need to consider immune-mediated hematological complications in children with unexplained anemia associated with nephritic syndrome.

Keywords: Acute poststreptococcal glomerulonephritis, autoimmune hemolytic anemia, complement-mediated hemolysis, direct antiglobulin test

INTRODUCTION

Acute poststreptococcal glomerulonephritis (APSGN) is one of the leading causes of acute nephritic syndrome in childhood, typically occurring 1–3 weeks after infections caused by nephritogenic group A beta-hemolytic streptococci.[1,2] APSGN is characterized by hematuria, edema, hypertension, oliguria, and, in particular, a transient decrease in serum complement component 3 (C3) levels.[1,2] Although APSGN is primarily a renal immune complex-mediated disease, it is known that streptococcal infections can lead to various immune-mediated sequelae outside the kidney.[3]

Hematological complications are not typical features of APSGN. Immune-mediated cytopenias, particularly immune thrombocytopenic purpura, have been reported rarely; however, the association of APSGN with autoimmune hemolytic anemia (AHA) is extremely rare.[4,5] The number of pediatric cases reporting this association in the literature is quite limited, leading to limited evidence regarding the evaluation and management of the disease.[4,5]

Warm-type AHA usually develops through immunoglobulin G (IgG) autoantibodies and is often associated with IgG positivity in the direct antiglobulin test, sometimes also with complement positivity.[6,7] In rare cases, only complement (C3d) positivity may be detected along with IgG negativity, and this serological pattern may be associated with clinically significant hemolysis.[8,9] Therefore, the occurrence of complement-mediated warm-type AHA in conjunction with APSGN presents a diagnostically challenging and clinically instructive picture.

This article presents a case of a 5-year-old male patient with APSGN and C3d-positive, IgG-negative warm-type AHA who responded well to corticosteroid treatment.

CASE

A previously healthy 6.5-year-old male patient was admitted to the hospital with complaints of pallor and fatigue that had

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persisted for a week. His history included an upper respiratory tract infection approximately 10 days prior to admission. The patient and his family had no known history of kidney or blood diseases.

On physical examination, the patient appeared pale and had mild scleral icterus. His blood pressure was 140/80 mmHg, which was above the 95th percentile for his age and height. No peripheral edema was detected. Abdominal examination revealed no hepatomegaly; however, abdominal ultrasonography showed borderline splenomegaly.

Laboratory tests revealed hemoglobin 7 g/dl, hematocrit 20%, mean corpuscular volume 76.9 fL, white blood cell count 15,800/μL, and platelet count 443,000/μL. The reticulocyte count was increased at 8%. Lactate dehydrogenase level was 284 U/L, total bilirubin was 2.1 mg/dl, and indirect bilirubin was 2.01 mg/dl, consistent with hemolysis.

The direct antiglobulin test was positive for complement component 3d and negative for IgG. Cold agglutinins and Donath–Landsteiner antibodies were negative. The peripheral smear showed polychromasia, anisocytosis, poikilocytosis, normoblasts, and spherocytes; no schistocytes were detected. Based on these findings, a diagnosis of AHA was made, and oral prednisolone therapy was initiated at a dose of 2 mg/kg/day.

On the third day of corticosteroid treatment, the patient developed gross hematuria, oliguria, and persistent hypertension. Urinalysis revealed 3+ proteinuria, 3+ hematuria, and 1+ urobilinogen. Urine microscopy showed numerous erythrocytes and erythrocyte casts. Serum urea level was 83 mg/dl, and creatinine level was 0.41 mg/dl.

Further evaluation revealed an antistreptolysin O level of 1500 IU/ml (normal <240 IU/ml). Serum C3 level was markedly low at 3 mg/dl, while complement component 4 level was normal. These findings supported the diagnosis of APSGN developing concurrently with AHA.

The patient was monitored with fluid restriction, antihypertensive treatment including amlodipine and enalapril, and continued corticosteroid therapy. The hemoglobin level increased by approximately 2 g/dl within two weeks. Corticosteroid therapy was gradually discontinued within six weeks. At follow-up, the patient was normotensive, her anemia had resolved, and her renal function had completely returned to normal.

DISCUSSION

APSGN is one of the most common causes of acute nephritic syndrome in childhood and develops following group A beta-hemolytic streptococcal infections.[1,2] The pathogenesis of the disease is related to immune complex deposition and complement activation and is characterized by transient hypocomplementemia.[1,2] In contrast, hematologic abnormalities are not typical features of APSGN.

Extrarenal immune complications of APSGN have been reported rarely. Among these, immune thrombocytopenic purpura is more frequently described, while the association of APSGN with AHA is extremely rare.[4,5] Most of the few pediatric cases reported in the literature involve male patients and have a history of recent streptococcal infection. This suggests a common immune mechanism triggered by streptococcal antigens.[3,5]

In the presented case, a rare serological pattern of warm-type AHA was observed in conjunction with APSGN. Only complement component 3d positivity was detected, along with IgG negativity in the direct antiglobulin test. Although warm-type AHA usually develops through IgG autoantibodies, in rare cases it may occur with only complement positivity.[8,9] In this case, since erythrocytes are coated only with complement, their recognition by macrophages may be delayed, and clinically significant hemolysis may develop despite atypical laboratory findings.[8]

The pathogenesis of complement-mediated, IgG-negative hemolysis has not been fully elucidated. It is thought that low-affinity or transient IgG antibodies initiate complement activation and then dissociate from the erythrocyte surface, leaving only complement particles behind.[9,10] Previous studies have reported that although more severe anemia may be observed in patients with complement-positive warm-type AHA, the response to corticosteroid treatment is generally good, especially in cases secondary to infection.[8,11]

Streptococcal infections can present with a wide variety of clinical manifestations.[12-16] In this case, the history of streptococcal infection, the development of APSGN, and the simultaneous onset of hemolytic anemia strongly support an immune-mediated mechanism. The rapid improvement of both clinical and laboratory findings after corticosteroid treatment strengthens the diagnosis of secondary AHA.[4,8]

CONCLUSION

This case contributes to the rare association of APSGN and AHA and demonstrates that immune-mediated hematologic complications must be considered in children with unexplained anemia and nephritic syndrome.

ETHICAL DECLARATIONS

Informed Consent

Informed consent was obtained from the legal guardians of the pediatric patient described in this report. Where developmentally appropriate, assent was also sought from the child. The inclusion of vulnerable populations in this study adhered to national and international ethical guidelines. Extra care was taken to ensure voluntary participation, understanding, and protection of participant dignity and autonomy.

Peer Review Process

This report underwent external peer review.

Conflict of Interest

The authors declare no conflicts of interest.

Financial Disclosure

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Author Contributions

Concept: S.T., Ş.T., Ü.A.T., M.A.; Design: S.T., Ü.A.T.; Control: S.T., Ş.T.; Resources: S.T., M.A.; Materials: Ş.T., M.A.; Data Collection and/ or Processing: S.T., M.A.; Analysis and/or Interpretation: S.T., Ş.T., M.A.; Literature Review: S.T., Ş.T., M.A.; Writing the Article: S.T., Ş.T., M.A.; Critical Review: S.T., Ş.A.

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