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Proteinuria in the nephrotic range in pregnant women. A single-center observational study.

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Abstract

Introduction: Physiological changes in pregnant women can be altered by the appearance of pathological phenomena such as proteinuria in the nephrotic range, relevant in the diagnosis of preeclampsia and glomerular disease. The objective of the present study was to describe the clinical characteristics and results of pregnant women with nephrotic proteinuria in a reference center in Cuba.

Methods: The present observational, prospective, longitudinal follow-up study for 12 weeks was conducted at the "Vladimir Ilich Lenin" General Hospital in Holguín, Cuba, between October 2020 and September 2022. All pregnant women with proteinuria in the nephrotic range were registered . The variables were age, body mass index at pregnancy detection, gestational age, African descent, number of pregnancies, serum creatinine, proteinuria in 24 hours at the onset of symptoms, and clinical history. Descriptive statistics are presented.

Results: 48 patients entered the study. White, primigravida pregnant women predominated; the average age was 24.8 years. The average gestational time was 31.8 weeks, and serum creatinine was 94.8 µmol/L. The main personal medical history was arterial hypertension and systemic lupus erythematosus. There was no statistical association between the age groups and the persistence of proteinuria. Pregnant women with proteinuria before 20 weeks maintained it after 12 weeks postpartum, defining it as kidney disease. Pregnant women with previous high blood pressure had a 2.2 times higher risk of preeclampsia.

Conclusion: In both causal groups (preeclampsia and kidney disease), there were maternal-fetal complications, highlighting induced abortion, preterm birth, intrauterine growth retardation, and low birth weight.

Keywords:

Proteinuria, Pregnancy, Nephrotic Range, Preeclampsia, Kidney Disease.

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Pregnancy is characterized by multiple physiological changes, the most important of which involve the formation of the placenta and the growth of the fetus. During a pregnancy or postpartum period in a healthy woman, kidney function presents essential anatomical and functional changes that determine the findings of studies and are critical to understanding the complexity of the pathophysiological alterations that can occur during pregnancy [1].

Hyperdynamics and modifications in tubular channels increase the excretion of proteins and amino acids (histidine, glycine, threonine, serine, and alanine). This explains why proteinuria sometimes appears in the urine of ordinary pregnant women progressively throughout pregnancy: in the first trimester, the average is 103 ± 49 milligrams (mg)/24 h; in the second trimester, it is 151 ± 40 mg/24 h; and in the third trimester, it is 180 ± 50 mg/24 h. In addition, it should be noted that high levels of proteinuria occur due to a reduction in the integrity of the glomerular barrier or a decrease in tubular absorption [1-3].

Pathologic proteinuria during pregnancy was defined as the presence of 300 mg of protein in 24-hour urine and a loss of more than five micrograms in a single sample. The nephrotic range is defined as the occurrence of proteinuria greater than 3.5 g in 24-hour urine [4].

Nephrotic-range proteinuria occurs in 12 to 25 per 1000 pregnancies. It is considered a cardinal characteristic of preeclampsia and the most common reason for which renal biopsy is performed during pregnancy, taking into account that it can also appear during pregnancy due to primary kidney disease or secondary systemic disorders [5].

When proteinuria is documented before pregnancy or before 20 weeks of gestation, it suggests underlying glomerular disease. The most common primary glomerulopathies are minimal change disease, focal segmental glomerulosclerosis, and membranous nephropathy. Other authors also included IgA nephropathy patients within this group. In pregnant women with these previous conditions, there is usually a transient worsening of hypertension, proteinuria, and renal function, especially when the proteinuria is nephrotic [6].

When proteinuria occurs after the 20th week of pregnancy, differential diagnosis is not always easy. However, primary nephrotic syndrome is rare in these circumstances, and preeclampsia is the most common cause. The importance of distinguishing these two diseases lies in the fact that the treatments used are different. In preeclampsia, the disease is not cured until pregnancy has ended, even if hypertension is controlled with drugs. When blood pressure levels decrease, placental perfusion decreases, with consequent risk for the fetus [3]. In preeclampsia, rapid delivery is required for its attenuation. In glomerular disease during pregnancy, however, treatment to prolong gestation may improve fetal outcomes. Complications of the nephrotic state include hypoalbuminemia as well as dire fetal and placental consequences combined with increased tissue fragility and increased thrombotic tendency [7].

Preeclampsia affects 5–7% of all pregnancies; it is one of the most significant gestational entities of interest and is conceptualized as a multisystem disorder characterized by a new onset of hypertension greater than or equal to 140/90 mmHg that occurs after 20 weeks of gestation or postpartum accompanied by proteinuria more than 300 mg/24 hours or maternal organ dysfunction and is believed to be the result of diffuse endothelial activation and dysfunction [8-10]. Preeclampsia is the leading cause of morbidity and mortality in pregnant women, accounting for more than 500,000 fetal deaths and 70,000 maternal deaths each year worldwide [8, 11]. A systematic analysis by the World Health Organization on the causes of maternal death has shown that hypertensive disorders constitute one of the leading causes of maternal death in developing regions, especially in Africa, Latin America, and the Caribbean. For example, in countries such as Mexico, they represent the first cause [4, 12]. In general, the prevalence of this disease can reach 26%. In Ecuador, in 2013, preeclampsia with significant proteinuria was classified as the leading cause of perinatal morbidity, accounting for 8.64% of infant deaths. It was also the leading cause of maternal death, accounting for 35.69% of maternal deaths in this country [13, 14].

It has been reported that preeclampsia increases the risk of suffering from chronic kidney disease and the risk of progressing to the final stages of kidney disease within ten years after pregnancy. It is also frequently associated with acute renal failure, which occurs in 1 in every 10,000 to 20,000 pregnancies in developed countries and underdeveloped countries in 1 in every 2,000 to 5,000 pregnancies [15, 16].

The evaluation of pregnant patients with proteinuria is challenging for both obstetricians and nephrologists. Those with worsening proteinuria (considered pathological) require additional monitoring due to potential adverse maternal consequences and associated severe neonatal complications, according to the International Society for the Study of Hypertension in Pregnancy [16- 18].

According to the 2021 edition of the Cuban Health Statistical Yearbook, in 2020, 44 deaths occurred due to glomerular and kidney diseases in women, for a crude rate of 10.7 per 100,000 inhabitants. Additionally, the maternal mortality rate in 2020 was 40 deaths/100,000 live births, 7.0% higher than that in 2019. The maternal mortality rate due to direct causes increased, while the rates due to indirect or late causes decreased [19].

No national registries or large-scale studies have identified an association between risk factors and proteinuria in the nephrotic range or between causes and obstetric outcomes in Cuba.

At the "Vladimir Ilich Lenin" General University Hospital, a national reference center for the results obtained over the years in the Maternal and Child Program, no research has been carried out on proteinuria in the nephrotic range in pregnant women, nor are there sufficient statistical data on all entities related to its appearance.

To answer the following research question: What are the clinical characteristics and outcomes of pregnant women with nephrotic proteinuria admitted to the Vladimir Ilich Lenin General University

Hospital? The present observational study proposes identifying risk factors for proteinuria during pregnancy.

Materials and methods

Study design

The present study is observational and prospective. The follow-up period was longitudinal at 12 weeks.

Scenery

The study was carried out in the obstetrics service of the Vladimir Ilich Lenin General Hospital in Holguín, Cuba, between October 2020 and September 2022.

Definition of the study population and the sample

The population consisted of all pregnant women admitted to the hospital who presented with nephrotic-related proteinuria. Through intentional sampling, 48 pregnant women who did not meet the exclusion criteria were selected.

Exclusion criteria

Patients who refused to participate in the study. Patients whose postpartum clinical and complementary follow-up was not possible.

Information sources

The author selected the variables to meet the objectives of the study. The data were subsequently recorded in an information collection model corresponding to the variables under analysis. The information was collected through a survey in interview mode with pregnant women, constituting the above primary source of information. The collection of clinical and laboratory data recorded in his hospital medical history was necessary, and complementary examinations were also required at the author's discretion; all of these examinations became a secondary source of data in the research.

Data collection technique

An extensive bibliographic and documentary search was carried out on the topic investigated, both in the international and national framework, and supported by online health networks and the Medical Sciences Information Center. It was accessed through search engines, using biomedical descriptors and structuring advanced searches on different web pages or through bibliographic reviews carried out in the databases of Cochrane, Bireme, Ecimed, Scielo, Hinari, Lilacs, PubMed, Clinical Key, ProQuest, EBSCOHost, National Statistics Office, Cuban medical journals, and Medline, among others.

Variables

The variables were age, body mass index at the time of pregnancy, gestational age in weeks, African descent, number of pregnancies, serum creatinine, and proteinuria within 24 hours at the onset of symptoms. Clinical history: arterial hypertension, systemic lupus erythematosus, scleroderma, primary glomerular disease, and sicklemic carrier.

Risk factors: The following variables were considered to be involved: obesity, smoking status, nulliparity, and a family history of glomerular disease.

Possible outcomes: Patients who developed preeclampsia or kidney disease were classified for analysis according to the following definitions:

Preeclampsia: a nephrotic syndrome that occurs after 20 weeks of gestation and is accompanied by high blood pressure.

Kidney disease: nephrotic syndrome that appears before 20 weeks of gestation as a de novo or previously known disease and in which proteinuria persists after 12 weeks postpartum.

Obstetric Complications: Complications were determined by what was collected from the maternal clinical history and were classified into maternal and fetal complications (unfavorable maternal and fetal outcomes):

Unfavorable maternal outcome: Induced abortion, preterm birth, eclampsia, HELLP syndrome.

Unfavorable fetal outcome: Intrauterine growth retardation, low birth weight: Newborn weighing less than 2500 g.

Statistical analysis

Descriptive statistics: The results are presented in statistical tables, where the absolute frequencies are presented, and the inferential statistics (relative frequency) are presented as percentages to describe the clinical characteristics and results of pregnant women with nephrotic syndrome. In addition, statistical correlation tests, specifically the chi-square test, were used for categorical variables. The statistical association was determined using the chi-square test with a 95% confidence interval between the previously described risk factors and the subset of patients with preeclampsia as the causal disease due to their greater significance.

Results

Participants

Forty-eight patients who met the inclusion criteria were included in the study.

Patient characteristics

The average age was 24.8 years, the average gestational age was 31.8 weeks, and 35 patients (72.9%) were primigravida.

The average proteinuria was 6.35 grams in 24 hours. Most patients (60.42%) had no relevant clinical history. The data are presented in Table 1.

Persistence of postpartum proteinuria

At 12 weeks after delivery, 7/48 patients (14.6%) had proteinuria more than 300 mg in 24-hour urine. No risks were significantly associated with age group for the persistence of proteinuria; these data are presented in Table 2. The persistence of proteinuria was associated with the gestational week in which it occurred; it persisted if it occurred before week 20 (P =0.001). The proteinuria was not persistent in all the patients who presented above week 20 (P =0.001) (Table 3).

Risk factors

The risk factors studied for the development of preeclampsia were not statistically significant. The control group consisted of patients with kidney disease, and the case group consisted of those diagnosed with preeclampsia. These data are presented in Table 4.

Maternal and fetal outcomes

Table 5 presents the maternal and fetal outcomes, the most relevant being preterm delivery.

Table 1 . Sociodemographic, clinical and laboratory characterization of pregnant women admitted who presented proteinuria in the nephrotic range.

Variables	Values
Age in years (Me ± SD)	24.77 ± 6.77
Body mass index at pregnancy uptake kg/m ^{2} (Me ± SD)	24.28 ± 3.11
Gestational age in weeks (Me ± SD)	31.76 ± 7.32
African descent	
White (%)	30 (62.5%)
Afro- Cuban (%)	18 (37.5%)
Pregnancies	
Primigesta *(%)*	35 (72.9%)
Multideed (%)	13 (27.1%)
Serum creatinine in µmol/L (Me ± SD)	94.82 ± 22.13
Proteinuria in g/24 hours (Me ± SD)	6.35±3.09
Clinical history	
Primary glomerular disease (%)	1 (2.08%)
Scleroderma (%)	1 (2.08%)
Arterial hypertension (%)	11 (22.92%)
Lupus erythematous systemic (%)	5 (10.42%)
Sicklemic carrier (%)	1 (2.08%)
No clinical history	29 (60.42%)

Me: average; SD: standard deviation.

Table 2. Distribution of pregnant women admitted with proteinuria in the nephrotic range according to maternal age and the persistence of proteinuria (≥300 mg/24 hours) after 12 weeks postpartum.

Maternal age (years)	Proteinuria 12 weeks postpartum				Total	Value - *P* * (OR)
	Persistent n=7 (14.6%)		Nonpersistent		(%)	
≤ 19	4	8.3%	10	20.8%	14 (29.2%)	0.078 (OR=4.13)
20 a 35	3	6.3%	27	56.3%	30 (62.5%)	0.245 (OR=0.38)
≥ 36	0	0	4	8.3%	4 (8.3%)	0.388 (OR=0.00)
Total	7	14.6%	41	85.4%	48 (100%)	N/A

* proof of chi square; A/N: no applicable

Table 3 . Distribution of pregnant women admitted with proteinuria in the nephrotic range according to gestation time at diagnosis and persistence of proteinuria.

Gestation time to diagnosis	Proteinuria after 12 weeks postpartum				Total (%)	*P*- value *
	Persistent		Nonpersistent			
≤ 11 weeks	2	4.2%	0	0	2 (4.2%)	0.001
12-19 weeks	5	10.4%	0	0	5(10.4%)	0.001
≥ 20 weeks	0	0%	41	85.4%	41(85.4%)	0.001
Total	7	14.6%	41	85.4%	48	N/A

* proof of chi square; A/N: no applicable

Table 4. Association between risk factors and the development of preeclampsia in pregnant women admitted to the "Vladimir Ilich Lenin" General Hospital with proteinuria in the nephrotic range. October 2020 to September 2022

Factors of risk	E.R. (n=7)	PE (n=41)	Total (%) (n=48)	Value - *P* * (OR)
Overweight or obesity	0	11	11 (22.9%)	0.119 (OR=ND)
Smokers	2	10	12 (25.0%)	0.813 (OR=0.80)
APP of Hypertension arterial	0	11	11 (22.9%)	0.479 (OR=2.20)
Creatinine serum elevated	4	25	29 (60.4%)	0.848 (OR=1.17)
Nulliparity	5	30	35 (72.9%)	0.923 (OR=1.09)
APP of preeclampsia former	0	8	8 (16.6%)	0.200 (OR=ND)
APF of disease primary glomerular either secondary	2	3	5 (10.4%)	0.088 (OR=0.19)

APF: Family pathological history. APP: Personal pathological history. ER: Kidney Disease. PE: preeclampsia.

Table 5. Distribution of complications (unfavorable obstetric or maternal/fetal outcome) presented by pregnant women admitted with proteinuria in the nephrotic range according to the cause: kidney disease or preeclampsia.

Outcome maternal/fetal unfavorable	ER (7)	%	EP (41)	%	Total
DM: Abortion caused	3	42.8%	0	0	3
DM: Childbirth preterm	4	57.1%	14	34.1%	18
DM: Eclampsia	0	0%	8	19.5%	8
DM: Syndrome HELLP	0	0%	1	2.4%	1
DF: Delay of the growth intrauterine	2	28.6%	5	12.2	7
DF: Low weight to the be born	2	28.6%	23	56	25

FD: fetal outcome. DM: Maternal Outcome. ER: Kidney Disease. PE: Preeclampsia

Discussion

A clinical, analytical, and sociodemographic characterization of the pregnant women admitted with proteinuria in the nephrotic range during the included period was carried out, obtaining results similar to those of other studies. Concerning age, an average of 24.8 ± 6.8 years was reached, which is similar to the average age at which a survey was carried out in 2017; kidney biopsies were taken from 26 pregnant women with nephrotic syndrome, whose maternal age was 27.6 ± 6.5 years [20]. Among those of African descent, 30 (62.5%) were white. Although African-American origin has been described as a risk factor for preeclampsia, the province of Holguín, the location of the study, is one of the Cuban provinces with a predominance of white people, 80% of whom were affected according to the last population and housing census in Cuba 2012.

Regarding the number of pregnancies, more than 50% of the pregnant women were primigravida: 35 patients (72.9%). The author considered that the above could be related to the tendency to decrease the fertility and birth rate observed in Cuba in recent years, which constitutes a commonly raised risk factor for preeclampsia.

Due to the hyperfiltration characteristic of pregnancy, creatinine levels are lower in pregnant patients than in nonpregnant patients, according to the Protocol for the Management of Hypertensive Disorders and Their Complications 2017. Accordingly, the Maternal and

Child Program governs creatinine levels in Vladimir Ilich Lenin Hospital. Average creatinine levels in pregnancy reach 0.8 mg/dL (70.72 µmol/L), and these figures are considered pathological above this value and even more so if the baseline values are doubled. As a result of the characterization, the creatinine values in these patients ranged between 94.82 ± 22.13 µmol/L. There was a predominance of high creatinine levels, requiring greater surveillance and strict control.

According to a study on proteinuria in the nephrotic range, the proteinuria values were 6.35 ± 3.09 g/24 hours, similar to Cuban research, which reported an average of 4.36 ± 0.76 g/day [5]. Additionally, a reference was made to the distribution of pregnant women with proteinuria in the nephrotic range according to associated chronic diseases of interest; among them, the highest prevalence was of preexisting arterial hypertension, with the appearance of proteinuria in these patients being due to preeclampsia.

Another significant finding was the association of proteinuria in the nephrotic range with kidney disease in 4 of the five patients with a history of systemic lupus erythematosus and only in one with preeclampsia.

Pregnancy and systemic lupus erythematosus are reciprocally affected. Pregnancy may increase the incidence of systemic lupus erythematosus and may have short- or long-term adverse effects on kidney function. Lupus nephritis is the third form of clinical presentation of lupus outside of pregnancy, but during pregnancy, it represents the most frequent clinical manifestation. This is a risk factor for pregnancy loss, especially in patients with kidney failure. Furthermore, they have a higher risk of restricted intrauterine growth and gestational hypertension (30–50%), including lupus nephritis patients with nonactive systemic lupus erythematosus [21].

A systematic review published in 2017 [22] determined that women with prior lupus nephritis, despite a preserved glomerular filtration rate, have higher rates of preterm birth and earlier-onset preeclampsia than women with lupus without renal involvement. It has been reported that there is a 15% increase in the odds of preterm birth for every 1 g/24-hour increase in proteinuria in each trimester [22].

The distribution of pregnant women admitted to the "Vladimir Ilich Lenin" General Hospital with proteinuria in the nephrotic range was analyzed according to age group and its relationship with the persistence of proteinuria, as shown in Table 2.

The highest frequency of the observed series was found in the 20-35 years group, in which 30 patients were included, accounting for 62.5% of the sample. In the age groups at high reproductive risk, namely, adolescence and advanced maternal age, a total of 18 patients were obtained, with a more significant number of adolescents. This is a critical point to highlight since, in primary health care, the number of family doctors could be increased to reduce pregnancies in these groups since all the risks that this entails are known.

There was no significant association between age and the persistence of proteinuria. However, pregnant women aged >19 years had an almost 5-fold increased risk of persistent proteinuria. Larger-scale studies are needed to determine the association between age and the incidence of persistent proteinuria.

The previous table includes data corresponding to the gestation period, the occurrence of proteinuria in the nephrotic range, and the pregnancy behavior twelve weeks after delivery, taking the persistence of proteinuria greater than or equal to 300 mg/24 hours as a reference.

Coincident with the findings of the bibliography consulted, 85.4% of the 41 patients who presented with proteinuria in the nephrotic range after 20 weeks of gestation had proteinuria normalized due to preeclampsia or arterial hypertension with superimposed preeclampsia. The remaining seven patients who had proteinuria in the nephrotic range before 20 weeks (2 before 12 weeks and five between 12 and 19 weeks) and who had persistent proteinuria remaining 12 weeks after delivery were defined as having previous or new kidney disease causing proteinuria in the nephrotic range.

In some cases, the distinction between kidney disease and preeclampsia can be made only retrospectively, as clinical signs of preeclampsia usually resolve within 12 weeks after delivery, while proteinuria due to underlying kidney disease does not, which is reflected in Table 6.

The calculated measurements demonstrated that gestational age at the time of diagnosis is significantly associated with the persistence of proteinuria. Specifically, a gestational age of less than 20 weeks at the time of proteinuria diagnosis was significantly associated with persistent disease. Regarding nephrotic syndrome during pregnancy, a gestational age of 18.6 weeks is suggestive of primary kidney disease [23].

Among the remaining risk factors, 11 patients were overweight and developed preeclampsia, which is consistent with the findings of other studies [24]; maternal overweight at the beginning of pregnancy contributed significantly to the incidence of preeclampsia, with an OR of 2.61 and more than 50% of the sample.

Obesity in women doubles the risk of preeclampsia for every 5 to 7 kg/m^2 increase in BMI before pregnancy [24]; this association is due to insulin resistance and undiagnosed diabetes [20]. Other authors believe that the obesity/hypertension relationship is due to the progressive increase in leptin. This protein, produced mainly in adipocytes, can regulate vascular tone and blood pressure. It is also responsible for the obesity/insulin resistance relationship, as it decreases insulin binding to insulin receptors, leading to increased blood pressure and preeclampsia [21].

Among the other risk factors, smoking represented 25% of the total number of patients, with ten patients developing preeclampsia. According to the literature consulted, no discussions associated this risk factor with preeclampsia. However, the damage it can produce is known to occur in endothelial tissue and even more so when related to other factors.

On the other hand, elevated creatinine values were present in 25 patients with preeclampsia. In 2019, a Chilean study obtained creatinine values less than 1.5 mg/dL, normal kidney function, and typical onset of blood pressure in pregnant women with nephrotic syndrome; moreover, worsening of proteinuria was associated with worse maternal and fetal outcomes. In other studies, it has been shown that elevated

creatinine levels are considered a risk factor for maternal complications [5].

Nulliparity has been established as a significant risk factor for the development of preeclampsia [22]; up to 85% of preeclampsia cases can occur in nulliparous women, who are 6 to 8 times more susceptible than multiparous women [23]. It is possible that during the first pregnancy, an aberrant immunological reaction is initiated by the first exposure to paternal and fetal antigens foreign to the placenta, contributing to this disorder [23]. However, the development of preeclampsia is supported by several theories, from placental ischemia with endothelial dysfunction to the toxicity-inducing function of very low-density lipoproteins to deficient immune adaptation and genetic imprinting; these last two factors could explain the development of this disease in patients who are homozygous for a relatively common susceptibility gene in their first pregnancy [24].

Although not all the variables available in the study could be used to distinguish between various pathologies that could give rise to proteinuria in the nephrotic range, the study refers to the fundus of the eye, Doppler of the uterine arteries, immunological studies (ANA, ANCA, LE, C3, C4 rheumatoid factor, etc.), biomolecular markers for preeclampsia, and kidney biopsy. However, other prospective studies should establish specific differences in lupus patients as a study group.

Conclusion

This study included predominantly white, primigravida pregnant women, and the average age was 24.8 years. The average gestational age at the onset of proteinuria was 31.8 weeks, and the average serum creatinine level was 94.8 µmol/L. The main personal pathological history revealed arterial hypertension and systemic lupus erythematosus. There was no significant association between age group and the persistence of proteinuria, but pregnant women aged 19 years or younger had an almost 5-fold greater risk of persistent proteinuria. In all patients who presented with proteinuria in the nephrotic range after 20 weeks of gestation, the level of proteinuria normalized due to preeclampsia or arterial hypertension with added preeclampsia. In turn, pregnant women with proteinuria before 20 weeks in all patients maintained detectable proteinuria after 12 weeks postpartum, defined as an exacerbation of previous or subsequent kidney disease.

Pregnant women with previous high blood pressure had a 2.2 times greater risk of developing preeclampsia than those without prior hypertension. In both groups with proteinuria in the nephrotic range (preeclampsia and glomerular disease), maternal-fetal complications occurred, highlighting induced abortion in pregnant women with kidney disease, as well as in both groups with preterm birth, intrauterine growth retardation, and low-weight at birth.

Abbreviations
ER: Kidney disease.

PE: Preeclampsia.

Supplementary information
The supplementary materials have not been provided.

Acknowledgments
Does not apply.

Author contributions
Susana María Castellanos Hechavarría: Data curation, Formal analysis, Funding acquisition, Research, Methodology, Project administration, Resources, Software, Writing – original draft.
Yadelys Gómez Rojas: Conceptualization, supervision, validation, visualization, writing: review and editing.
Lissette María Osorio Ferrer: conceptualization, supervision, validation, visualization, writing: review and editing.
All the authors read and approved the final version of the manuscript.

Financing
The studies, laboratory tests, and intradialytic measurements constituted the regular activity of the obstetric unit and were not a cost to the patients. The authors provided the administrative costs of this research.

Availability of data or materials
The data sets generated and analyzed during the current study are not publicly available due to participant confidentiality; however, they may be shared upon reasonable academic request.

Statements

Ethics committee approval and consent to participate
The Scientific Council and the Research Ethics Committee of the "Vladimir Ilich Lenin" General Hospital of Holguín, Cuba, approved the study. The ethical principles outlined in the Declaration of Helsinki were used to conduct the research. The well-being of people was maintained as a priority concerning the exclusive interest of science as formulated in the Universal Declaration on Bioethics and Human Rights; with complete confidentiality of the data and taking into account the necessary ethical elements, the participants signed an informed consent form.

Consent for publication
Patients who do not publish patient photographs, CT scans, or specific radiographic studies were not needed.

Conflicts of interest
The authors declare no conflicts of interest.

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