

# Plasma colloid osmotic pressure in preeclampsia. Review of the Mexican literature 1997-2018

## *Presión coloidosmótica del plasma en la preeclampsia. Revisión de la literatura mexicana 1997-2018*

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### Abstract

In Mexico, plasma colloid osmotic pressure has been a key issue in the study of pregnant women for more than two decades. Clinical investigations have allowed to know their values in the open population, as well as in women with normal pregnancy, physiological puerperium, severe preeclampsia, HELLP syndrome, and eclampsia. The relationship of plasma colloid osmotic pressure with mean arterial pressure (Briones index), capillary leak syndrome and the accumulation of fluid in serous cavities (pleural effusion, and ascites) have also been reported. We reviewed the database of PubMed, The Cochrane Library, OVID, Science Direct, Google Scholar, Artemisa, LILACS, and IMBIOMED from 1997 to 2018 with the following keywords: serum albumin, plasma colloid osmotic pressure, capillary leak syndrome, Briones index, pleural effusion, ascites, severe preeclampsia, HELLP syndrome, eclampsia, and obstetrics critical care. Inclusion criteria were systematic reviews, meta-analysis, clinical controlled trials, and articles with evidence-based medicine methodology with strong recommendations. We included 12 Mexican articles. The objectives of the present investigation were to review the medical literature on plasma colloid osmotic pressure in preeclampsia reported from 1997 to 2018, describe the treatment with human albumin and the perspectives of the research in the following years.

**Key words:** Plasma colloid osmotic pressure. Capillary leak syndrome. Briones index. Severe preeclampsia. HELLP syndrome. Eclampsia.

### Resumen

En México, la presión coloidosmótica del plasma ha sido un tema clave del estudio de la mujer embarazada por más de dos décadas. Las investigaciones clínicas han permitido conocer sus valores en población abierta, mujeres con embarazo normal, puerperio fisiológico, preeclampsia severa, síndrome HELLP y eclampsia. También se ha reportado la relación de la presión coloidosmótica del plasma con la presión sanguínea (índice de Briones), síndrome de fuga capilar y la acumulación de líquido en cavidades serosas (derrame pleural, ascitis). Revisamos la base de datos PubMed, The Cochrane Library, OVID, Science Direct, Google Scholar, Artemisa, LILACS e IMBIOMED de 1997 a 2018 con las siguientes palabras clave: albúmina sérica, presión coloidosmótica del plasma, síndrome de fuga capilar, índice de Briones, derrame pleural, ascitis, preeclampsia severa, síndrome HELLP, eclampsia y cuidados críticos en obstetricia. Los criterios de inclusión fueron revisiones sistemáticas, meta-análisis, ensayos clínicos controlados y artículos con metodología de medicina basada en evidencia con recomendacio-

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nes sólidas. Incluimos 12 artículos mexicanos. Los objetivos de la presente investigación fueron: revisar la literatura médica de la presión coloidosmótica del plasma en preeclampsia reportada de 1997 a 2018, describir el tratamiento con albúmina humana y las perspectivas de la investigación en los siguientes años.

**Palabras clave:** Presión coloidosmótica del plasma. Síndrome de fuga capilar. Índice de Briones. Preeclampsia severa. Síndrome HELLP. Eclampsia.

## Introduction

The plasma colloid osmotic pressure (PCOP) is the force exerted by plasma proteins and electrolytes contained in their molecules; it is the force that serves to conserve water and solutes in the intravascular space. Its effect preserves liquids and solutes when proteins are found in the interstitial space of body tissues. The intravascular and interstitial hydrostatic pressure opposes their forces to the colloid osmotic pressure of both compartments. A slight local imbalance resulting from all pressures favors the continuity of the tissue microcirculation which makes it possible for the supply of water, electrolytes, and nutrients to be sufficient to satisfy the metabolic needs of the cells, tissues, organs, apparatuses, and systems of the organism<sup>1</sup>.

In normal pregnancy, the value of PCOP is reduced by the dilution of blood proteins (albumin and globulins mainly) due to the increase in plasma volume which has not only physiological but also therapeutic implications<sup>2,3</sup>. In preeclampsia, PCOP modifications are more important because the endothelial lesion and alterations in the architecture of the arterial, arteriolar, and capillary walls favor capillary leakage of proteins into the interstitium or into the renal tubules. More cases of severe preeclampsia or HELLP syndrome can be accompanied by thrombosis inside the microvasculature in different maternal organs<sup>4,5</sup>.

Capillary leak syndrome manifests clinically as the abnormal accumulation of fluid and proteins, mainly albumin, in soft tissues such as skin, fatty tissue and muscle (edema), in the serous layers (pleural effusion, pericardial effusion, and ascites), and in the interstitial space of the vital organs (cerebral edema, pulmonary edema, and hepatic congestion)<sup>4-7</sup>. The pathophysiological mechanism of abnormal proteinuria in preeclampsia ( $\geq 300$  mg/day) develops practically in the same scenario, but at the glomerular level<sup>8</sup>. The proteins leave the capillaries, enter the mesangial channels, accumulate in the urinary space of the glomerulus, and appear in the tubular fluid in various amounts which can be determined with relative ease<sup>9</sup>.

PCOP can be calculated when the plasma concentration of total proteins, albumin, and globulins is known<sup>10,11</sup>. Circulating fibrinogen also participates in the generation of PCOP, but to a lesser degree so it is generally not taken into account for its calculation. When the value of PCOP is known, its relation with mean arterial pressure (MAP) can be estimated to measure the capillary leak syndrome, the rate is known as the Briones index<sup>12</sup> (Table 1).

## Mexican literature

In Mexico, PCOP values have been reported in women with normal pregnancy, physiological puerperium, severe preeclampsia without and with edema, severe preeclampsia and anasarca, severe preeclampsia with pleural effusion and/or ascites, HELLP syndrome, and eclampsia.

The first report of the PCOP during normal pregnancy and the physiological puerperium dates back to 1997 from a study conducted by Briones et al.<sup>13</sup>. The authors studied 50 non-pregnant women, 50 women with normal pregnancy, and 50 women with a physiological puerperium, all of them residents of Toluca, Mexico. They found that the average of the PCOP was 26.9,  $24.4 \pm 4.4$ , and 17.7 mmHg, respectively. In the year 2000, Briones et al.<sup>12</sup> studied the relationship between PCOP with MAP and its usefulness for measuring capillary leak syndrome in 87 preeclamptic patients versus 50 pregnant women without preeclampsia. The authors found that the Briones index (the PCOP/PAM ratio) can identify the presence of capillary leak syndrome when its value is  $>0.11$ .

In the year 2006, Briones et al.<sup>14</sup> studied a group of six pregnant patients with acute renal failure undergoing peritoneal dialysis versus 32 patients who did not require it. Maternal hemodynamic measurements included the calculation of PCOP. They found that the PCOP of dialyzed patients was  $16 \pm 2.7$  and  $16 \pm 4.39$  mmHg in women without dialysis treatment.

In the year 2010, Vázquez-Rodríguez<sup>15</sup> reported PCOP, Briones index, and ascites in 225 pregnant patients with preeclampsia-eclampsia. The PCOP and

**Table 1. Formulas**

Formula of Landys-Pappenheimer

$$\text{PCOP mmHg} = 2.38(\text{TP}) + 0.138(\text{TP})^2 + 0.00957(\text{TP})^3$$

$$\text{PCOP mmHg} = (\text{serum albumin g/dL} \times 5.54) + (\text{globulins} \times 1.43 \text{ g/dL})$$

$$\text{Briones Index} = \text{PCOP mmHg} / \text{MAP mmHg}$$

PCOP: plasma colloid osmotic pressure, TP: total proteins, MAP: mean arterial pressure.

the Briones index were calculated as a total group and in three categories: (a) severe preeclampsia without the HELLP syndrome 196 cases, (b) severe preeclampsia with the HELLP syndrome 26 cases, and (c) eclampsia three cases. They found that the mean PCOP of all the patients was  $20.14 \pm 2.52$  mmHg; in 148 cases (65.78%) it was normal (average  $21.54 \pm 1.60$  mmHg); and in 77 (34.22%) it was low (mean  $17.55 \pm 1.71$  mmHg) ( $p = 0.058$ ). There was no difference between the three categories ( $p > 0.05$ ). The average of the Briones index of all the patients was  $0.18 \pm 0.03$ ; in 87 cases (38.67%) it was normal (mean  $0.22 \pm 0.01$ ); and in 138 (61.33%) it was low (mean  $0.16 \pm 0.01$ ) ( $p = 0.07$ ). There was no difference between the three categories ( $p > 0.05$ ). Ascites was documented (mean  $627.27 \pm 85.21$  ml) in 11 patients (4.89%). The correlation of the PCOP versus the Briones index was 0.55, PCOP versus ascites -0.03 and the Briones index versus ascites -0.43. For the authors, the most important findings were the low values of PCOP in 34.22%, the Briones index with statistical significance in 61.33% and the negative correlation of both parameters with ascites.

In the year 2011, Vázquez-Rodríguez and Velóz-Martínez<sup>16</sup> reported the frequency of pleural effusion and ascites and the correlation of PCOP with renal filtration in 92 pregnant women with severe preeclampsia. The frequency of collections was 43.48% (ascites 16 cases, pleural effusion 12 cases, and ascites with pleural effusion 12 cases). The mean PCOP in patients without and with collections was different ( $20.12 \pm 2.16$  vs.  $18.78 \pm 2.58$  mmHg,  $p = 0.009$ ) as well as renal filtration ( $111.69 \pm 37.61$  vs.  $95.27 \pm 34.22$  ml/min/1.73 m<sup>2</sup> body surface,  $p = 0.03$ ). The correlation of PCOP was negative with all collections (ascites - 0.25, solitary pleural effusion - 0.29, ascites with combined pleural effusion - 0.02, and pleural effusion combined ascites - 0.30). The correlation of renal filtration and ascites was - 0.01, versus pleural effusion alone - 0.13, and versus combination of ascites with pleural effusion - 0.27 and - 0.67,

**Table 2. Classification of vascular damage in preeclampsia**

Degrees of injury	Findings
0	Normal appearance
1	Swelling, detachment and death of endothelial cells. It is the image described as "endotheliosis"
2	Anterior lesion plus disruption of the basal layer of the endothelium, evidence of perivascular leakage of fluid, and erythrocytes in small numbers
3	Previous injuries plus alterations of the muscular layer, frank vascular hemorrhage
4	Previous injuries plus alterations of the elastic fibers, adventitial layer
5	Previous injuries plus thrombosis or thrombosis as a solitary finding

respectively. The authors concluded that the frequency of collections was very high (43.48%) with a weak negative correlation of PCOP with fluid collections and renal filtration.

In 2014, Rodríguez-Tovar et al.<sup>17</sup> compared the effect of parenteral administration of crystalloid solutions, starch in 6% solution and human albumin in 25% solution on PCOP of 106 pregnant preeclamptic patients. The baseline PCOP was  $19.34 \pm 2.79$  mmHg and at the end of all interventions  $17.09 \pm 2.40$  mmHg ( $p = 0.18$ ). Specifically, there were no changes with the administration of starch ( $p = 0.35$ ), albumin with starch ( $p = 0.20$ ), and albumin alone ( $p = 0.61$ ). When patients ( $n = 23$ ) received only crystalloid solutions, PCOP showed a reduction with statistical significance (baseline  $20.49 \pm 2.38$  vs. final  $17.56 \pm 2.29$  mmHg,  $p = 0.0001$ ). For the authors, the most relevant findings were that treatment with crystalloid solutions markedly reduced PCOP, while patients who received albumin in 25% solution had the most discreet drop. Both therapeutic modalities failed to improve baseline PCOP.

In the year 2016, Garzón-García and Vázquez-Rodríguez<sup>18</sup> conducted a pilot study that included 30 pregnant patients with severe preeclampsia undergoing cesarean section. During the surgery a biopsy of the parietal peritoneum was taken to study the structural changes of arteries and capillaries and their correlation with PCOP. The structural changes of the arteries and capillaries of the parietal peritoneum were classified using an ordinal scale by degree of injury (Table 2). The mean of the PCOP was  $18.79 \pm 2.64$  mmHg. No PCOP differences were found between the different degrees of injury ( $p > 0.05$ ).

**Table 3. Recommendations for the administration of human albumin in preeclampsia**

Parameter	Clinical status	Indication
Serum albumin	Prepartum and puerperium	<2 g/dL
Proteinuria	Prepartum and puerperium	>2 g/24 h
PCOP	Prepartum	<20 mmHg
	Puerperium	<18 mmHg
Briones Index (PCOP/MAP)	Prepartum and puerperium	<0.11

PCOP: plasma colloid osmotic pressure, MAP: mean arterial pressure.

In the year 2018, Vázquez-Rodríguez et al.<sup>19</sup> compared the PCOP of 372 patients with severe preeclampsia, 172 women with permanent residence in Ciudad Obregón, Sonora region, located 40 m above sea level and 200 resident patients of Mexico City, located at 2250 m above sea level. The average of the PCOP of the Ciudad Obregón patients was  $18.10 \pm 2.18$  mmHg (limits 11.88 and 21.80) while for the residents of Mexico City it was  $18.93 \pm 2.72$  mmHg (limits 10.31 and 23.94), the comparison showed a significant difference ( $p = 0.0016$ ) especially at the expense of the albumin concentration ( $p = 0.0208$ ). Due to the fact that the patients residing in Ciudad Obregón were characterized by being younger and with greater weight, height, and body mass index than the patients from Mexico City, the authors think that the findings indicate that the values of serum albumin and PCOP may be conditioned by nutritional factors. They also suggested that it may be convenient to carry out regional measurements to establish the value of the PCOP according to the nutritional characteristics of the patients and their geographical area.

### Therapy with human albumin

PCOP has not been considered in the international and Mexican literature as a finding of severity of preeclampsia because there is not enough evidence<sup>20-22</sup>.

However, in Mexico, the administration of human albumin to correct PCOP is used relatively frequently. In our setting, it is applied to preeclamptic patients with decreased serum albumin and PCOP values, but who are accompanied by generalized edema, anasarca, massive pleural effusion, and/or ascites to an extreme degree during pregnancy or in the postpartum period (Table 3).

Before the administration of human albumin, correction of the circulating volume is required with the cautious application of crystalloid solutions to rule out pre-renal azotemia and ensuring that the urinary tract is permeable. It is administered as a 50 ml bottle containing human albumin in 25% solution in an intravenous infusion for 1 h followed by a dose of 40 mg of furosemide, this is repeated every 8 h<sup>23</sup>. The intention is to improve the redistribution of fluids and solutes from the interstitial space to the intravascular compartment to provide renal perfusion and thereby increase urine output. The therapy is based on an old recommendation of Fliser et al.<sup>24</sup> and the so-called furosemide stress test published recently by Chawla et al.<sup>25</sup>. Patients who are candidates for human infusion of albumin must remain in an intensive care unit for the immediate treatment of any eventuality<sup>23,26</sup>. The consensus of the experts is that acute tubular necrosis is the most frequent cause of little or no response to treatment<sup>25</sup>. Clinical studies whose design is aimed at demonstrating the effect of the restoration of PCOP are necessary before recommending the use of generalized human albumin.

### Perspectives

Undoubtedly, the contribution of the descriptive studies from autopsy material and biopsies of the organs of patients with preeclampsia, eclampsia, and HELLP syndrome has historically contributed to the knowledge of vascular alterations due to the disease. At present, the authorization to carry out postmortem studies in Mexico and in the world is restricted and a biopsy performed during pregnancy is only carried out in selected cases. In addition to these two situations, the fact that there is no animal model of experimentation to study preeclampsia is factors that have not advanced in the investigation of the structure of maternal blood vessels.

The idea of the researchers that the issue is exhausted is an unfortunate thought, the possibility of innovation exists. For example, based on the descriptions of the medical literature of the last century and the most recent decades, Vázquez-Rodríguez<sup>18,27</sup> has proposed a classification of vascular damage in preeclampsia, which orders the histopathological findings by degrees of injury. It has been called the classification of "preeclamptic vasculopathy" ranging from Grade 0 or normal appearance to Grade 5 that includes thrombosis (Table 2).

Because the majority of patients with severe preeclampsia, eclampsia and HELLP syndrome undergo

**Table 4. Future research**

Vascular structures	Topic
Glycocalyx	Integrity, changes in its electrical charge and molecular composition in preeclampsia
Intimate layer and middle layer	Intima-media thickness as a criterion of vascular involvement in a peritoneal biopsy, and equivalent to the ultrasonographic measurement of the common carotid artery
Intimate, basement membrane, middle layer	Differential stains, deposits of immune complexes, molecular changes, and hormonal effects
Middle layer, muscular layer	Affectation of the contractile apparatus, vascular hyperreactivity, and effect of drugs
All layers	Preeclampsia and the aging process and vice versa

cesarean section for gestational interruption and the involvement of serous agents in the disease has been documented, a biopsy of the parietal peritoneum has been proposed by Vázquez-Rodríguez<sup>18,27</sup>. It can be a useful tool to study arterial and capillary vessels in preeclamptic patients, especially in the most severe cases or with diagnostic doubts (Table 4).

Peritoneal biopsy also has other areas of opportunity. The intima-media thickness originally described in studies with ultrasound of the arterial vessels of the neck and arm of patients with cardiovascular risk factors can be studied with greater property in a sample of the parietal peritoneum<sup>28</sup>. Similarly, peritoneal biopsy can provide the necessary material to study histopathological data suggesting atherosclerosis or accelerated vascular aging in preeclampsia, a mechanism similar to that of atherosclerosis in patients with diabetes, chronic kidney disease, peritoneal dialysis, dyslipidemias, and pro-inflammatory diseases that persist for years or due to advanced age<sup>29</sup>.

The vascular findings could predict if patients with postpartum hypertension with cardiovascular risk factors could evolve toward chronicity, even when they are not patients with preeclampsia. Simulators of preeclampsia such as chronic arterial hypertension, systemic lupus erythematosus, and autoimmune vasculitis of various types may also be studied through an intra-partum peritoneal biopsy when the cesarean section is performed. The differential diagnosis based on histopathology and immunohistochemical studies would solve the most difficult cases of diagnostic doubt<sup>18,27</sup>.

The endothelium is the first maternal organ affected by preeclampsia and its hormonal and molecular

mediators present in the bloodstream. It has been documented that the maternal plasma of the preeclamptic patient has a direct cytotoxic effect on the endothelium of capillaries and arterioles at a systemic level and that a state of imbalance in favor of pro-coagulation increases its thrombotic effect in the most severe cases. The endothelial lesion has been well documented, but the mechanism by which the glycocalyx, the interface located between the luminal surface of the endothelial layer and the bloodstream, can deteriorate is unknown. Specifically, glycocalyx changes can be known in relation to the natural history of the disease and the administration of parenteral fluids and drugs<sup>30</sup>.

Finally, it would be interesting to know the status of Starling forces and the role of the glycocalyx model in transvascular exchange in preeclamptic patients, mainly at the onset of the disease. The results could also guide the selection of a better intravenous fluid therapy to preserve the circulating volume and prevent tissue hypoperfusion in general, but without damaging the glycocalyx<sup>31</sup>.

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## Conclusions

Preeclampsia is a disease of placental origin with an effect on the small arterial and capillary vessels of the maternal economy and its complications. In the last two decades, Mexican literature has contributed with results of clinical studies on the subject of PCOP in preeclampsia. Now the opportunity to know the vascular changes in more detail is projected. The contribution of peritoneal biopsy to study the ultrastructure of the arteries and capillaries can be the gateway to address issues of preeclampsia that has been little explored.

## Conflicts of interest

The authors declare no conflicts of interest.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this study.



**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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