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Clinical Trials in Pregnant Women with Preeclampsia


Abstract

Preeclampsia (PE) is the leading cause of preterm birth by medical indication when associated with premature detachment of placenta normoinserita, and Intrauterine growth restriction (IUGR) is associated with high perinatal morbidity and mortality and long-term sequelae. The main problem of PE is threefold: the diagnostic difficulty, the complicated interrelationship of the pathophysiological processes, and the vulnerability of the maternal-fetal binomial to the therapeutic interventions. The approach for management with PE is preventing its late occurrence in pregnancy. The key to preventing PE is knowledge of the factors that trigger the pathophysiological processes that culminate in the presentation of PE. Understanding the developmental characteristics of the placenta in pregnancy at high risk for PE is essential for understanding the pathophysiology and developing strategies for prevention. When deciding that the population of study is a group of pregnant women, the first ethical criteria that need to be reviewed are those aimed at the protection of the fetus. There are no specific guidelines on how to assess fetal well-being during pregnancy routinely in the clinic, and this deficiency is shifted to clinical research with pregnant women.

Keywords: preeclampsia, eclampsia, pregnancy induced-hypertension, complications in pregnancy women
1. Introduction

Preeclampsia (PE) is the leading cause of preterm birth by medical indication when associated with premature detachment of placenta normoinserta, and IUGR is associated with high perinatal morbidity and mortality and long-term sequelae. It has been described that standardization in the management of health services and the use of clinical practice guidelines is associated with a reduction in adverse outcomes, and a fundamental part of the management of severe PE includes a complete evaluation of the mother and the fetus. Despite the advances in medicine, the frequency of this syndrome has not changed, and globally its incidence ranges between 2 and 10% of pregnancies. The World Health Organization (WHO) estimates that the incidence of PE is seven times higher in developing than in developed countries (2.8–0.4%). In Mexico, it is estimated that PE is a major cause of maternal and perinatal morbidity and mortality. In Jalisco alone, maternal deaths increased to 57.14% from 2011 to 2014, placing this state in fourth place at the national level in terms of maternal deaths, during 2015 [1]. Because it is a heterogeneous associated idiopathic syndrome to endothelial damage, so far there is no effective treatment that reduces the morbidity and mortality of this pathological entity, so it is necessary to reinforce prevention. In this area, only the use of calcium supplements and acetylsalicylic acid (ASA) appears to be a recommendation, albeit with controversial results [1, 2].

The main problem of PE is threefold, the diagnostic difficulty, the complicated interrelation-ship of the pathophysiological processes, and the vulnerability of the maternal-fetal binomial to the therapeutic interventions.

2. Pregnant women, scientifically complexed population

There are various concepts about the characteristics of vulnerable populations; however, it is generally accepted that a vulnerable group is one whose ability to protect their own interest or grant their consent is physically, psychologically, or socially compromised. Since the development of ethical principles in research, children, psychiatric patients, prisoners, and pregnant women have been included in this group; however, in recent years it has been intended to remove pregnant women from this group. The National Institutes of Health (NIH) through the Office of Research on Women’s Health recommended as early as 2010 that pregnant women should be considered as a scientifically complex rather than vulnerable group, this being for the reason that this group has the same capacity and autonomy for decision making as its nonpreg-nant counterparts, including the decision of whether or not to participate in a clinical trial [3].

Scientific complexity arises from the special physiological conditions of pregnancy and from the ethical considerations of the balance between maternal well-being and fetal well-being.

Pregnancy is accompanied by important physiological changes and their knowledge is an element of great value for the proper management of the obstetric patient. Practically, all the body’s system of the pregnant woman is adapted to house the product, among them are changes at the ocular, musculoskeletal, skin and mucous, hepatic, hematological, renal, and gastrointestinal levels. The most relevant changes occur at the uterine level, systemic vascular
resistance is reduced due to high flow and low resistance circuit in the uteroplacental circulation. In pregnancy, uterine blood flow significantly increases to allow perfusion of intervillous placental spaces and fetal development. The trophoblast invades the uterine spiral arteries; vascular smooth muscle cells are lost and replaced by the fibrinoid material, converting them into large dilated blood vessels allowing greater perfusion of the placenta [4]. These changes pose a challenge for the researcher as they make it very difficult to define not only the possible therapeutic results of an intervention, but also to adapt the intervention to these new changes that are not present in nonpregnant women. In a pathological condition such as preeclampsia, this may represent a greater challenge, because of restrictions on research in a physiological pregnancy, ignorance or doubts about the effects of the intervention on the organism, or pathological adaptations that may affect the intervention that is intended to be performed are greater.

The ethical complexity is established in the possibility that the intervention applied in key phases causes a teratogenic risk or that affects the adaptation of the product to extrauterine life, and more worrying, the possibility of long-term toxicity. This is why it is necessary that preclinical teratogenicity studies have been completed prior to the intervention in pregnant women. Also, it is recommended to start the new interventions after the 12th week of gestation, when the organogenesis is finished and finally, it is recommended to follow the fetus and newborn [5]. However, these special considerations do not seem to be sufficient, as there are currently two forms of research in the group of pregnant women: the first consists of interventions unrelated to pregnancy that may benefit only the mother [3]. It seems that the previous recommendations were formulated with this type of research, since the use of thalidomide has contemplated the possibility of developing drugs that may attenuate different discomforts during pregnancy. The clinical investigation currently has to verify that the pharmacological interventions do not cause damage to the product and not only benefit the mother. The second type of research concerns interventions that may potentially benefit the mother and her fetus [3]. This aspect is more related to the development of pharmacological interventions for pathologies in pregnancy, specifically speaking of preeclampsia, the treatments are not indicated at the same time for the mother and for the fetus. Betamimetics used to prevent preterm birth are not intended to treat the mother and may even complicate maternal health. In contrast, depending on the severity of hypertension, the drugs could have a toxic effect on the fetus. These two aspects should be considered when deciding to experiment with a new therapeutic product or scheme [5].

3. Fetal well-being in the clinical trial

When deciding that the study population is the group of pregnant women, the first ethical criteria that need to be reviewed are those aimed at the protection of the fetus. Generally, investigations of pregnant women involving an intervention or experimental procedure such as in PE cases, should not expose the embryo or fetus to a greater risk than the minimum, except when the use of the intervention or procedure is justified for saving the life of the mother. However, in addition to a deep and sufficient knowledge of the intervention that is proposed to apply, there is no strategy to evaluate during the course of research the side effects on the
product. Although maternal-fetal medicine is currently a fact, with several diagnostic imaging and biochemical resources, with established therapeutic procedures, there is no consensus on what tests are necessary to perform and monitor the product during investigations in pregnant women. Even experts do not dare to indicate any fetal diagnostic procedure, within the clinic in the management of pathological pregnancies, but it is at the discretion of the attending physician the use of some diagnostic or therapeutic techniques [6].

There are six most generalized methods to know and evaluate fetal well-being [7]:

1. Maternal evaluation of fetal activity. It consists of the count by the mother of the number of times fetal movement occurs. Although the fetal movement count is a recommendation that is made to every pregnant woman, there is no cutoff point when abnormal movement is considered abnormal, some clinicians mark the alarm in less than 10 fetal movements perceived per day, others when no movements are perceived within 2 h. This form of assessment of fetal well-being presents a false-positive rate, since it depends on the subjectivity of the mother.

2. Test without stress. It consists of the evaluation of fetal heart rate in relationship to uterine contractions. Although it has a low false-negative rate (0.19–1%), its high rate of false positives (55%) makes it a test with minimal benefits, and its counterpart, the stress test, in which it is administered by infusion intravenous oxytocin, is contraindicated in high-risk situations.

3. Biophysical profile. It is a test composed of the evaluation of five parameters, fetal heart activity, fetal respiratory movements, fetal thick movements, muscle tone, and volume of amniotic fluid. Although its false-negative rates are very low (0.07%), its false-positive rate is only lower than that of the stress-free test, and has not shown any difference in terms of fetal death, cesarean indication, and under Apgar score. In addition to being a dependent operator test, factors that may alter outcomes include hypoxemia, gestational age, steroid administration, magnesium sulfate administration, and labor; five factors that occur frequently in pregnant women with PE.

4. Modified biophysical profile. It is the combination of the stress-free test with the biophysical profile. Although it requires less time and experience for its realization, makes its result more reliable, its false-positive and -negative rates are similar to the two tests separately.

5. Fetal Doppler ultrasound. The evaluation consists in measuring by ultrasound the velocity of blood flow in the fetal vessels, usually the umbilical artery. Out of all of the above, Doppler has been evaluated with the most rigorous clinical trials and although it does not show a benefit in terms of fetal death in high-risk pregnancies, it has become an effective test in the reduction of fetal morbidity and mortality in high-risk pregnancies, being this an indication for its use. The use of Doppler in pregnant women with high risk of PE can be a predictive tool combined with serum biomarkers; this strategy is still being validated but promising.

6. Evaluation of fetal lung maturity. It consists the evaluating the presence of surfactant factor in the amniotic fluid. It is a useful evaluation when it is necessary to determine the best time to interrupt the pregnancy when the risk of continuing it is greater. Due to the fact
that in PE the treatment consists of the interruption of pregnancy, to be able to prolong it until reaching the fetal maturity, becomes one of the most difficult aspects of the management to avoid the fetal morbidity-mortality, reason why it is to make sure that the fetus counts with pulmonary maturity to resist extraterine life has become essential.

Although these tests and diagnostic interventions are the most used in the clinic, the amount of imaging tests, serum markers, and procedures with maternal-fetal medicine is higher; however, many of the tests have not shown their value, they could be useful and applicable reason why they require to be studied, especially those that allow predicting the presentation of complications or diseases such as PE. Among the currently available tests are the evaluation of both fetal DNA and the cells that make up the placenta, even in an experimental way, it is possible to attenuate or increase gene expression through miRNAs, not only for diagnostic purposes, but also for possible therapeutic applications in the future.

The American Congress of Obstetricians and Gynecologists states that the evaluation of fetal well-being may be appropriate for pregnancies with an increased risk of fetal involvement; however, there are no comprehensive trials demonstrating the benefit of all tests and their potential indications. On the other hand, experts recommend carrying out tests of fetal well-being in cases of diabetes, uterine growth restriction, and hypertension [7].

As we can see that there are no specific guidelines on how to evaluate fetal well-being during pregnancy routinely in the clinic, and this deficiency is translated into clinical research with pregnant women. As mentioned before, although one of the principles of research in pregnancy is to maintain the integrity of the product, there are neither guidelines nor recommendations on which tests to apply and when to ensure the safety of the fetus. From the above, we can infer that most clinical trials involving pregnant women have not been able to guarantee or know with certainty the fetal well-being. So how is it possible to monitor fetal well-being in a clinical trial? How can we evaluate adverse effects on the product? And if there is no strategy to assess at least fetal well-being, is it ethical to allow the participation of pregnant women in clinical trials? It is up to the researcher to decide the degree of safety with which he plans to conduct his research, and in the absence of additional tests to ensure fetal well-being, using those available is the most reasonable. However, we should not be satisfied with the analysis of the structural function to guarantee the innocuousness of an intervention, it is necessary to find strategies that in fact allow to evaluate not only the welfare, structural integrity, and fetal vitality, but also to value the whole range of possible adverse effects, both acute and chronic, that may be occurring as a result of new pharmacological interventions or procedures.

4. Clinical research in women pregnant with PE

Pregnancy is a physiological condition inherent in almost all species and life; however, it is one of the lesser known states and a field of research that just begins to grow, because at the beginning of research with pregnant women, a series of events occurred that negatively marked research in this population.
Research is now making its way into the subject of pregnancy and its pathologies in order to have a better understanding of physiological processes and to reduce maternal-fetal morbidity and mortality. However, despite the intentions and efforts of researchers, little is known. In the context of PE, it has been possible to trace its origin to the inadequate invasion of the trophoblastic villi on the vascular bed of the uterine spiral arteries, little is known about the cause of this inadequate adaptation of the uteroplacental vascular system [8]. Moreover, we are in complete disbelief about why some women develop PE and others do not. There is no effective diagnostic test to predict who will have PE, the best biomarkers have poor predictive power, the best chance to achieve prevention so far arises from the combination of Doppler ultrasound with some of the serum markers, which have been implemented, nevertheless, only demonstrate efficacy once the first evident changes of PE are presented, when it is no longer possible to avoid the development of the disease [9]. A real opportunity for prevention of PE would arise from a marker that would allow us to know with great certainty, which women are at risk of having PE, even before the pregnancy is carried out. The best predictive tool we have are the risk factors that have been determined by both prospective and retrospective studies, but are only able to predict 30% of women who develop PE [9], there is even a larger group of the population that develops PE with no previous risk factors. On the other hand, from the group of women who develop PE, one part shows severe PE and another group develops eclampsia, and again it is not possible for the treating doctors to determine who and how they evolve to more serious stages.

In women with severe PE, who present it before fetal viability, maternal stabilization is recommended before interruption of pregnancy. Once treatment is established, close monitoring is required to identify the presence of serious complications of PE. Despite efforts to treat PE, treatment is symptom-based and focused on controlling blood pressure. In regard to the time of delivery, gestational age should transfer to the maximum possible. However, in severe PE, in addition to antihypertensive treatment, termination of pregnancy is recommended if it is greater than 34 weeks. If the pregnancy is less than 34 weeks and the mother and product are stable, the pregnancy should be continued with administration of corticosteroids. Currently, there are multiple criteria for better management of PE, but the only cure for PE is termination of pregnancy. This results in a difficult decision for the physician and the mother because of the psychological burden, and the social and economic morbidity [8].

The results of medical interventions have failed to significantly decrease the morbidity and mortality of PE. The main reason for this failure could be the multifactorial origin of pathogenic processes that lead to the development of PE. Therefore, the approach for management of patients with PE is preventing its late occurrence in pregnancy. The key to prevention of PE is knowledge of the factors that trigger pathophysiological processes that culminate in the presentation of the PE. However, efforts to understand the origin of these processes are still poorly or incompletely understood. There is a lack of knowledge because the approach to study this population may be unethical compared with diseases of nonpregnant women [10]. The multifactorial origin of PE and difficulty of carrying out an investigation in the early stages of pregnancy, because it can endanger the mother and fetus, have made research difficult. Understanding the developmental characteristics of the placenta in pregnancy at high risk for PE is essential for understanding the pathophysiology and for developing strategies of prevention [8].
5. Current state of research about PE

There are currently 236,008 clinical trials registered in clinicalTrials.gov, from which only 3% are focused on pregnancy, and among them 6.4% are about PE. Of all clinical trials dedicated to PE, 47.9% focus on strategies to improve treatment, 22.2% of the clinical trials aim to improve the diagnosis or its establishment in the early stages, and 16.7% aim to establish the utility of new biomarkers, for both diagnostic and monitoring. Finally, only 10.7% of the clinical trials registered until February 1, 2017 are focused on the prevention of PE (Figure 1).

Another aspect that should be taken under consideration is that more than half of the clinical trials directed to PE are carried out in regions classified as first world such as Europe and North America, whereas research in the rest of the world only constitutes 40%, despite the fact that developing countries are the ones that bear the greatest burden of morbidity and mortality caused by this disease (Figure 2).

In our times, PE has a worldwide relevance and it has been increasing over the years. Clinical trials with the objective of reducing the morbidity and mortality of this pathology have also increased over time. The previous chart denotes some of the terminated trials registered in clinicaltrials.gov, many of which have certain limitations that we were able to observe (Table 1).

In the study titled, “L-arginine and antioxidant vitamins during pregnancy to reduce pre-eclampsia”, there is little coherence between the objective and the design of the study. Although...
it is known that the production of nitric oxide and l-arginine as the main substrate of nitric oxide synthase is involved in the pathophysiology of PE, the study design is directed at the effect of l-arginine that has on the development of PE; however, levels of l-arginine are not evaluated at any moment, neither its nitrates nor nitrites, being the reason why this design cannot help reach the hypothesis. In addition, the main inclusion criteria appeared to be having a high-risk profile for developing PE; however, high-risk factors such as diabetes, autoimmune diseases, and hypertension in pregnancy and kidney diseases are not considered as inclusion criteria, and these factors combined with a history of risk of developing PE in previous pregnancies, increase up to nine times the risk of developing PE. Another mistake that can be found in their design is when analyzing the main conclusion and the way the intervention was carried out, the conclusion states that the supplementation of l-arginine and vitamins reduces the incidence of PE; nevertheless, in the results it can be appreciated that the group that only received the food-bar containing the vitamins did not have a significant reduction in the risk of developing PE. Meaning that the mayor contributing factor for the reduction of PE was indeed l-arginine and not the combination of l-arginine/vitamins, and these would have been more notorious if a supplementation group taking only l-arginine was added [11].

In the study titled “Usefulness of Extracorporeal Removal of sFLT-1 in Women with Very Early Severe Preeclampsia (ADENA)”, at first instance we are led to appreciate that the primary outcome of the study is about early severe PE; however, later, we appreciate that the intention is improving perinatal death as the primary outcome. The first comment worth mentioning is that using words such as “improving” in an investigation study may be imprecise, it is better to use terms such as “reducing” for this instance. Moreover the levels of sFLT-1 are not per say an inclusion criteria for deciding whether or not to perform apheresis, even by being quantified before and after the intervention, those women with high levels of sFLT-1 could perhaps have a
<table>
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<tr>
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<td>L-Arginine and Antioxidant Vitamins during Pregnancy to Reduce Preeclampsia</td>
<td>To test that a relative deficiency of L-arginine, precursor of nitric oxide (NO) by the enzyme NO synthase (NOS), reduces the development of preeclampsia in high-risk pregnancies</td>
<td>Pregnant women with a history of a previous pregnancy complicated by preeclampsia, or preeclampsia in a first degree relative, whom are deemed to have an increased risk of recurrence of the disease, were studied from 14 to 32 weeks of gestation and followed until delivery</td>
<td>Supplementation with medical food-bars containing L-arginine plus antioxidant vitamins, antioxidant vitamins alone or placebo</td>
<td>Supplementation during pregnancy with a medical food containing L-arginine and antioxidant vitamins reduced the incidence of preeclampsia in high-risk pregnancy</td>
</tr>
<tr>
<td>Usefulness of Extracorporeal Removal of sFLT-1 in women with very early severe Preeclampsia (ADENA)</td>
<td>The removal of s-Flt1 improves perinatal death in women with very early severe preeclampsia</td>
<td>Women with singleton pregnancy having severe preeclampsia at 23–25 6/7 weeks of gestation</td>
<td>Apheresis for extracorporal removal of sFlt-1</td>
<td>Does not have a result</td>
</tr>
<tr>
<td>Oral Progesterone and Low Dose Aspirin in the Prevention of Preeclampsia</td>
<td>Low-dose aspirin combined with progesterone will decrease the risk of preeclampsia in pregnant women with history of preeclampsia in a previous pregnancy</td>
<td>Pregnant patients with a previous history of preeclampsia in the immediate prior pregnancy</td>
<td>Aspirin 81 mg once a day orally, progesterone 200 mg twice daily</td>
<td>Does not have a result</td>
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<tr>
<td>Safety and Efficacy of RLX030 in Pregnant Women with Preeclampsia</td>
<td>Part 1: To assess the safety and tolerability of different doses of RLX030, when given to pregnant women with preeclampsia. Part 2: To assess whether an optimal dose of RLX030 can prolong pregnancy in women with preeclampsia</td>
<td>Pregnant women in 28 weeks (0 days) and 33 weeks (+4 days) of gestational age with a diagnosis of preeclampsia or superimposed preeclampsia requiring hospitalization</td>
<td>RLX030 15 μg/kg/day IV for 72 h</td>
<td>Not enough information was provided to analyze because the study was stopped after three patients were enrolled</td>
</tr>
<tr>
<td>CPAP in Preeclampsia</td>
<td>To assess the effects of nasal CPAP in pregnant women (24–37 gestational weeks) with preeclampsia</td>
<td>Women with 24–37 weeks of pregnancy with Singleton pregnancy, primiparous and primigravid diagnosis of preeclampsia</td>
<td>Continuous Positive Airway Pressure Ventilation (CPAP)</td>
<td>Does not have result</td>
</tr>
</tbody>
</table>


Table 1. Current state of clinical trials about PE.
greater benefit, reason why stabilizing grades at first instance could help the obstetrician make a better clinical decision. Finally, although its justifiable not using a control group, this type of design (before and after), not having a reference group, leads to a lower internal validity [11].

In the study titled “Oral Progesterone and Low Dose Aspirin in the Prevention of Preeclampsia”, the main inclusion criterion is having a history with preeclampsia. Nevertheless, other factors of high risk were not taken account. Even though the study propounds that a deficiency of progesterone could lead to PE and in consequence, supplementation with progesterone could reduce the incidence of PE, serum values as an indicator to identify patients whom could benefit with progesterone supplementation were not taken into account. The comparison between before and after instead of vs the placebo group is also an inconvenient [11].

In the study titled “Oral Progesterone and Low-Dose Aspirin in Preeclampsia Prevention,” the main inclusion criterion is the antecedent of PE in previous pregnancies; however, as in the previous study, other factors that increase the risk are not taken into account. The study assumes that a deficiency of progesterone could be the cause of PE, this argument seems to be the rationale to reduce the incidence of PE using supplementation with progesterone; but in the study, they did not take serum values in consideration as a marker to indicate which patients could benefit from supplementation. This study, as the previous one, also lacks the comparison against a placebo group, creating the same limitations [11].

In the study entitled “Safety and Efficacy of RLX030 in Pregnant Women with Pre-Eclampsia” proposed by the company NOVARTIS did not have sufficient information to perform an analysis, because of premature termination of the study [11].

In the study entitled “CPAP in Preeclampsia”, the main objective is the evaluation of fetal well-being using nasal continuous positive airway pressure (CPAP) as a basis to increase fetal oxygenation; however, monitoring fetal movements is a scarce strategy to evaluate fetal well-being and it could be enhanced, according to the advances in fetal medicine to allow us to get closer to knowing the well-being of the fetus. The study did not make a distinction on the severity of PE, and if a clinical benefit of using CPAP is demonstrated, a distinction on the severity might be useful for clinical decisions. Therefore, the rationale to use CPAP is not clear [11].

In several studies, narrowing gestational age as inclusion criteria perhaps increases internal validity; however, the results cannot be extrapolated to other groups [11].

It is worth noting that the protocols registered in clinical trial go through variations during the study, which go unnoticed.

6. Transference of scientific knowledge to clinical practice persist in LAG

One of the most important advantages of basic research is the possibility to transfer knowledge to improve clinical practice. However, in the case of PE, new information
regarding new biomarkers and new opportunities of intervention emerge every year, but these are not implemented by the treating physicians. Moreover, clinical practice guidelines are lagging too, and many years pass before a new intervention reaches the level of recommendation within them. On the one hand, this occurs because the information that is generated seems to be isolated and fragmented, there is no body or work team or expert committee that focus their efforts on trying to solve the problem or on generating a line of research on the subject. Another part of the transforming knowledge problem is that for this to be carried out it is necessary that the information obtained may be applicable to different populations at different times and with different characteristics, this is very complex to achieve in the first place because, as mentioned previously, there is no focus group to this and separated efforts generate a bias in the study population. Another bias that impedes transfer is that the risk factors presented by each population are different in the developed countries than those in the developing world, so information generated on the one side is not necessarily applicable in other parts of the world. Because the origin of PE is not well understood, the approaches with which the different studies are developed differ, while some may determine that the cause is oxidative stress, some others may argue that the cause is genetic. The truth is that so far it is considered multifactorial and because of this the international guidelines are more discreet about which recommendations to accept, in the sense of being able to verify which actions will have an evident weight in clinical practice.

Finally, one of the most worrying aspects that delay the transfer of knowledge is the lack of medical update on the subject. A very obvious example is that in practice, physicians do not intentionally seek pregnancies with a high risk of PE, and when a patient is classified with high risk, the first action of the doctor is an expectant management, without any intervention, although in the guidelines of clinical practice the administration of acetylsalicylic acid, calcium, and l-arginine is recommended, this happens because evidence of acetylsalicylic acid’s efficacy in reducing the risk is contradictory, while calcium intake is reserved for those women with low risk and low calcium intake, and l-arginine, although it is part of the Canadian guide, no dosage or time is specified.

Other evidence in the lack of management of the subject in some specialists is the lack of communication they generate with patients who are at high risk. Patients are not informed of their situation and expectant management “poor surveillance” continues even after the patient develops PE, which is when the symptomatic management begins, and it seems that the physicians are waiting for a complication to occur, to make the decision of taking a more active management. It is true that during the 1st weeks of the PE, there are not many recommendations, and that most focus on the final stages in which fetal viability can be achieved, but this same reason should be what drives medical doctors to have a closer monitoring in research opportunities and new information to improve the outcome of the pregnancy, remembering that once PE is presented, there is no curative treatment, beyond the interruption of pregnancy. Efforts should be directed at preventing the occurrence of PE or, failing at that, occurring late in pregnancy.
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