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Effect of Short-Time BelAge™ Prescription on Pregnancy and Risk Preeclampsia

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ABSTRACT

Introduction: The aim was to determine if one month taking BelAge™ in the second trimester of pregnancy could reduce the risk of preeclampsia.

Methods: From April 2019 to July 2020, a non-blinded, prospective, randomized, study was performed inviting women in the second trimester of pregnancy to take 3 g of BelAge™ once daily for one month. The control group received only the nutritional assessment. Relative risk (RR) to develop preeclampsia with 95% confidence interval (CI) was calculated using the Social Science Statistics online software, considering a significant statistical value a P-value < 0.05.

Results: 144 patients from the BelAge™ group (mean age 23.6 ± 9.7), and 99 from the control group (mean age 22.1 ± 8.6) were included, finding differences basal systolic blood pressure (P = 0.03), final diastolic blood pressure (P = 0.002) and final mean blood pressure (P = 0.001). Preeclampsia was developed by 18 patients in the BelAge™ group versus ten patients in the control group, RR 1.2 (95% CI, 0.60–2.57, P = 0.57).

Conclusion: A short-time BelAge™ prescription in the second trimester of pregnancy was enough to reduce the DBP, but did not reduce the risk of developing preeclampsia.

Keywords: BelAge™ diastolic blood pressure, preeclampsia, relative risk.

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1. Introduction

Preeclampsia complicates 3%–5% of pregnancies after 20 weeks of gestation in developed countries [1] but 16.7% of pregnancies in the developing world.[2] In fact, it is the leading cause of maternal death in developing of countries and a major contributor to maternal and perinatal morbidities. In Mexico, the incidence of preeclampsia is about 7.6 [3] and accounts for up to 34% of all maternal deaths, being the leading cause of pregnancy complications and deaths.[4]

Preeclampsia is a diverse, multiorgan group of related disease processes with a highly variable presentation but generally includes the combination of maternal hypertension and proteinuria. Currently, the American College of Obstetricians and Gynecologists integrates preeclampsia with and without severity characteristics,[5] previously known as mild and severe preeclampsia.[6]

The evolution of this disease is unpredictable; it progresses from a moderate state to another preeclampsia with severity data or even eclampsia in just a matter of minutes. Thus, preeclampsia must be recognized as a continuous disorder. Because the cause of preeclampsia is unknown, medical therapy is empirical and only aims to prevent or treat complications. Maternal and perinatal outcomes can be improved by proper and timely treatment. However, timely pregnancy interruption is the only and final curative treatment.[7]

An imbalance in the redox state in preeclampsia has been constantly observed,[8,9] i.e., women with preeclampsia have an increased production of free radicals and, at the same time, a decrease in several important antioxidants that generate oxidative stress and consequently leads to damage to the entire class of important molecules, such as unsaturated fatty acids, DNA, and proteins, as well as lipid peroxidation.[10] It has been known lately that, in addition to the direct damage that free radicals can inflict on the molecules, imbalance in the redox state can alter the normal function of various signaling pathways that possess the physiological functions necessary to maintain the homeostasis of organisms.[11]

BelAge™ (Sanki, Japan) contains Orisod V, a complex of polyphenols and metabolites from olive fruit and rosemary leaf. Orisod V is standardized in carnosic acid, carnosol, flavonoid acid, hydroxytyrosol, oleacein, oleuropein, rosmarinic acid, and tocopherols; it also contains more than 300 metabolites. The recommended dose is to dilute 1 sachet a day in 16 ounce (≈ 500 ml) of water.[12]

This project aimed to determine the effects of a short period of BelAge™ administration and nutritional management in patients who were in their second trimester of pregnancy and at a high risk of developing preeclampsia compared to those high-risk patients with only nutritional management.

2. Methods

2.1 Study design and setting

From April 2019 to July 2020, a non-blinding, prospective, randomized, clinical study was conducted at the "Mónica Pretelini Sáenz" Maternal-Perinatal Hospital (HMPMPS), Health Institute of the State of Mexico, Toluca, Mexico, to evaluate the effects of 1 month supplementation of BelAge™ on pregnancy. The matched variables were age and weeks of gestation.

2.2 Sample size calculation and recruitment of patients

Patients were recruited in Nutrition Consultation using the following inclusion criteria: pregnant patients at 20–24 gestational weeks (GW), patients with risk factors for developing preeclampsia (age > 40 years primiparous/multiparous, teenage mother, family history of preeclampsia (mother/sister), personal own history of preeclampsia and previous pregnancy of not less than 34 GW, multiple pregnancies, intergenic period greater than 10 years, body mass index (BMI) > 30 kg/m2,

and autoimmune disease). The exclusion criteria were as follows: patients presenting some language deficit, patients with previous diagnosis of hypertension or renal failure, or patients with ongoing pregnancies with congenital disorders. Patients who did not return to be attended at the end of their pregnancies in our Hospital were excluded from the final analysis.

2.3 Sample

Sample size calculation was performed with the next formula:

Using an Excel sheet with the input of Zα = 1.96 for 95% confidence, Zβ = 0.842 for a power of 80%, a difference (d) in the diastolic blood pressure (DBP) equal to or greater than 5 mmHg with an standard deviation (S) assumed of 12 mmHg, 90.45 ≈ 90 patients were needed per group. S value was obtained from a previous study with pregnant women in the second trimester that showed a range from 3.3 to 13.9 mmHg.[13] To ensure success with the antioxidant supplement, it was decided to add 60 more initial doses anticipating possible losses in the follow-up.

2.4 Intervention

The selected participants of the experimental group were asked to take 3 g of BelAge™ diluted in 500 mL of water once daily for 1 month. Clinical monitoring was performed as usual every month. Nutritional assessment was conducted on each patient to provide a meal plan based on the required kilocalorie based on the ideal weight before pregnancy, this last nutritional intervention without BelAge™ was implemented in the control group.

2.5 Routine measurements

Besides the general characteristics of the patients (age, pregnancies, vaginal deliveries, cesareans, abortions, weeks' gestation, as a hospital routine, weight (kg) and height (m) were measured using a weight scale (SECA 711) and a mechanical column scale (SECA 220), respectively. The patients were classified according to their pregestational BMI (kg/m^2) as follows: underweight, normal weight, overweight, and obese. Ideal weight without pregnancy (%) was calculated using reference tables. Gestational weight gain (kg) from the second to the third trimesters was also calculated. Blood pressure was registered using an automatic sphygmomanometer (Riester, Germany), and gestational diabetes mellitus was diagnosed *via* 75-g oral glucose tolerance test.
Finally, the frequency of the next maternal-perinatal complications were registered from the medical files: preeclampsia, gestational diabetes mellitus, premature rupture of membranes, gestational hypertension, intrauterine growth restriction, small fetus, maternal death, big fetus, threatened preterm labor, obstetric hemorrhage, thrombocytopenia, pyelonephritis, fetal death.

2.6 Statistical analysis

Descriptive statistics (mean ± 1 SD) were used to characterize quantitative variables. The Kolmogorov test was performed to determine the normality of the variables and based on the Gaussian distribution of the variables, either Student's T test or the Mann Whitney U test were employed to compare them. Categorical variables were expressed as percentages, and chi-squared test was used to compare them. Relative risk (RR) with 95% confidence interval (CI) was calculated to see the possible protective effect of the use of BelAge™ . All statistical analyses were conducted using the Social Science Statistics software, considering a significant statistical value of $P < 0.05$.

2.7 Ethical considerations

This project was approved (code 2020-04-682) by the Research Ethics Committee of the HMPMPS with current registration with the National Bioethics Commission (CONBIOETICA) and the Research Committee of the same hospital with current registration in the Federal Commission for Protection Against Health Risks.

This study was conducted in compliance with the protocol, Good Clinical Practice Standards, Nuremberg Code, Declaration of Helsinki (Fortaleza, Brazil, 2013),
Belmont Report, and associated regulations. Written informed consent was obtained from each patient, and according to the intervention level, it was considered a study of greater than minimal risk.

3. Results

A total of 144 patients from the BelAge™ group (mean age 23.6 ± 9.7) and 99 from the control group (mean age 22.1 ± 8.6) maintained the programmed clinical visits until the end of their pregnancy (Table 1 presents the patients' general characteristics). At the start of the recruitment, the distribution of women per BMI classification in the BelAge™ group was as follows: underweight, 4 (2.7%); normal weight, 82 (56.94%); overweight, 40 (27.77%); and obese, 18 (12.5%). In the group with only nutritional advice, the distribution was as follows: 6 (6.06%), 44 (44.44%), 31 (31.31%), and 18 (18.18%), in the same order as above.

Table 1. General characteristics of the patients, basal and at the end of pregnancy

Variable	Belage + Nutritional advice (N = 144) Mean ±SD	Nutritional advice (N = 99) Mean ±SD	P
Age (years)	23.6 ± 9.7	22.1 ± 8.6	0.21
Pregnancies (frequency)	1.8 ± 1.3	1.5 ± 1	0.10
Vaginal deliveries (frequency)	0.5 ± 1	0.3 ± 0.7	0.04
Cesareans (frequency)	0.2 ± 0.5	0.2 ± 0.5	0.80
Abortions (frequency)	0.1 ± 0.5	0.1 ± 0.3	0.50
Weeks' gestation (weeks)	21.3 ± 1.5	21.2 ± 1.5	0.87
SBP (mmHg)	99 ± 8.3	102.1 ± 10.5	0.03
DBP (mmHg)	62.9 ± 9.3	63.4 ± 9	0.61
MBP (mmHg)	74.9 ± 8	76.3 ± 8.7	0.23
BMI (kg/m^2)	25 ± 5.1	25.6 ± 5.6	0.33
Ideal Weight without pregnancy (%)	100.6 ± 23.9	103.5 ± 24.2	0.23
Weeks of delivery	38.2 ± 2.5	38.4 ± 2.4	0.26
SBP (mmHg)[a]	107 ± 22.4	107.5 ± 19	0.21
DBP (mmHg)[a]	68.9 ± 12.8	72.4 ± 10.9	<0.01
MBP (mmHg)[a]	81.6 ± 15.6	84.1 ± 12.7	<0.01
BMI (kg/m^2)[a]	27.3 ± 5.7	27.6 ± 6.9	0.47
Weight Gain (kg)	5.1 ± 6.7	5.2 ± 8.2	0.06

a: at the end of pregnancy. BMI: Body Mass Index, DBP: Diastolic Blood Pressure, MBP: Mean Blood Pressure, SBP: Systolic Blood Pressure.

In the BelAge™ group, the identified risk factors were age (114, 9.16%), family history of preeclampsia (30, 20.83%), previous preeclampsia (24, 16.66%), cardiopathy (2, 1.38%), and eclampsia (2, 1.38%). In the group with only nutritional advice, the risk factors were age (79, 79.79%), family history of preeclampsia (20, 20.20%), and previous preeclampsia (19, 19.19%). Through the chi-squared tests, the risk factor "previous preeclampsia" gave a result of 0.2569 (P = 0.61); the same test for the risk factor "family history of preeclampsia" showed a value of 0.0143 (P = 0.90).
In relation to the quantitative variables, through the Kolmogorov test, it was found that all data was not normally distributed; thus using the Mann-Whitney U test, differences were observed in the number of vaginal deliveries (P = 0.02), basal systolic blood pressure (P = 0.03), final DBP (P = 0.0002) and final mean blood pressure (MBP) (P = 0.00012). The most common complications are presented in Table 2. In this line and following the most important aim of this project, the RR to develop preeclampsia contrasting the BelAge™ and nutritional advice vs only nutritional advice was of 1.2 among them (95% CI, 0.60–2.57, P = 0.57).
It is important to note that of the 18 cases of preeclampsia in the BelAge™ group, 7 had a family history of preeclampsia, and 7 also suffered from preeclampsia in a previous pregnancy. On the contrary, in the group with nutritional advice, only one patient who developed preeclampsia had a family history of preeclampsia, and one had suffered from this obstetric complication in a previous pregnancy.

Table 2. Frequency of main perinatal complications per group

Complications	Belage + Nutritional advice (N = 144)	Nutritional advice (N = 99)	RR	95% CI	P
Preeclampsia	18	10	1.24	0.60 to 2.57	0.57
Gestational Diabetes Mellitus	15	7	1.47	0.62 to 3.48	0.38
Premature Rupture of Membranes	13	9	0.99	0.44 to 2.23	0.99
Gestational Hypertension	9	2	3.09	0.68 to 14.01	0.14
Intrauterine growth restriction	5	3	1.14	0.28 to 4.68	0.85
Small fetus	6	5	0.82	0.26 to 2.63	0.74
Maternal death	2	0	3.45	0.17 to 71.06	0.42
Big fetus	1	1	1.37	0.13 to 14.95	0.79
Threatened preterm labor	1	0	2.07	0.08 to 50.28	0.65
Obstetric hemorrhage	0	1	0.23	0.01 to 5.58	0.37
Thrombocytopenia	0	1	0.23	0.01 to 5.59	0.37
Pyelonephritis	0	1	0.23	0.01 to 5.59	0.37
Fetal death	0	1	0.23	0.01 to 5.59	0.37

4. Discussion

The importance of oxidative stress in preeclampsia-induced endothelial dysfunction has prompted the development of therapeutic approaches with the aim of restoring the redox equilibrium.[14] Thereby, numerous studies have focused on antioxidant supplementation as a treatment for preeclampsia. For example, different alternatives have been evaluated as antioxidants, the most studied being vitamins C and E as possible protectors against preeclampsia. However, an exhaustive review of the studies seeking to evaluate their utility has concluded that the experimental evidence does not support the use of such vitamins to achieve that target.[15]

There are many more substances that have been postulated as antioxidants to control preeclampsia, such as inositol,[16] astaxanthin,[17] and ergothioneine,[18] but until now, a recommendation for the use of antioxidants cannot be done with the available information of all the tested components.[19]

A previous study evaluated a mixed antioxidant supplementation of vitamins A (1000 IU), B6 (2.2 mg), B12 (2.2 µg), C (200 mg), and E (400 IU), folic acid (400 µg), Cu (2 mg), Zn (15 mg), Mn (0.5 mg), Fe (30 mg), Ca (800 mg), Se (100 µg), and N-acetylcysteine (200 mg), and a lower rate of preeclampsia has been observed.[20] Another potential supplement is a mixture of natural components and antioxidant properties.

Until now, there is scarce information regarding antioxidants and their possible effects on the DBP in pregnant women at risk of developing preeclampsia. Hofmeyr et al. published that a high-dose calcium supplementation (≥ 1 g/day) may reduce the risk of preeclampsia (low-quality evidence).[21]

Most of the studies that explore the effects of antioxidants on blood pressure to prevent preeclampsia have been done in animals.[22,23] Surprisingly, in relation to the antioxidant BelAge™ there are no publications to compare our results, so in some way, it is a pioneering study.

Finally, it is important to note that, in women who had already suffered from preeclampsia in a previous pregnancy, it is extremely difficult to prevent a newer case. This means that in order to avoid a second event such complication, it is necessary to implement something else other than nutritional advice and antioxidants. In addition, it should be noted that the patients in both groups gained only 5 kg in 17 weeks; in the same population, the average weight gain in total pregnancy was about 10 kg.[24,25] Whether longer time of taking BelAge™ could limit the weight gain in patients who had a high BMI at the start of pregnancy remains to be elucidated.

To some extent, the hypothetical weight gain contention using BelAge™ could represent a tool for reducing the intensity of the inflammatory process that carries danger during pregnancy. The quantification of the cytokines while using BelAge™ is a pending issue that needs to be solved in the near future.

A limitation of this study is the relatively low number of pregnant women who participated. Notwithstanding, the evidence obtained from the analysis indicates that the DBP could be a mainstay clinical parameter to be checked in women with risk factors for developing preeclampsia. Further studies on the quantification of antioxidant enzymes during

pregnancy while receiving BelAge™ needs to be conducted in a wider population and for a longer period of time.

5. Conclusion

BelAge™ did not show reduction in the risk to develop preeclampsia but could be useful in lowering DBP during pregnancy, and a better control of blood pressure could reduce the risk of developing preeclampsia; however, this hypothetical effect might be limited in cases of a previous pregnancy with preeclampsia or when there is a family history of preeclampsia.

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References

1. Filipek, A., & Jurewicz, E. (2018). Preeklampsja – choroba kobiet w ciąży [Preeclampsia - a disease of pregnant women]. *Postepy biochemii, 64*, 232–229. doi: 10.18388/pb.2018_146
2. Osungbade, K. O., & Ige, O. K. (2011). Public health perspectives of preeclampsia in developing countries: implication for health system strengthening. *Journal of pregnancy, 2011*, 481095. doi: 10.1155/2011/481095
3. Canto-Cetina, T., Coral-Vázquez, R. M., Rojano-Mejía, D., Pérez Godoy, S., Coronel, A., & Canto, P. (2018). Higher prepregnancy body mass index is a risk factor for developing preeclampsia in Maya-Mestizo women: a cohort study. *Ethnicity & health, 23*, 682–690. doi: 10.1080/13557858.2017.1315367
4. [Ministry of Health, National Center for Gender Equity and Reproductive Health, Mexico]. [Technical Guideline. Prevention, diagnosis and management of preeclampsia / eclampsia]. 4a. Ed. 2007. Available from: http://www.salud.gob.mx/unidades/cdi/documentos/PREECLAMPSIA_ECLAMPSIA_lin-2007.pdf
5. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. (2013). *Obstetrics and gynecology, 122*, 1122–1131. doi: 10.1097/01.AOG.0000437382.03963.88
6. Turner J. A. (2010). Diagnosis and management of pre-eclampsia: an update. *International journal of women's health, 2,* 327–337. doi: 10.2147/IJWH.S8550
7. Romero-Arauz, J. F., Morales-Borrego, E., García-Espinosa, M., & Peralta-Pedrero, M. L. (2012). Guía de práctica clínica. Preeclampsia-eclampsia [Clinical guideline. Preeclampsia-eclampsia]. *Revista medica del Instituto Mexicano del Seguro Social, 50*, 569–579.
8. Mendieta Zerón, H., Parada-Flores., A., Amaya Chávez, A., & Domínguez García, MV. (2013). Oxidative stress in preeclampsia, more than enzymes. *Revista Latinoamericana de Hipertensión, 8*,25-28.
9. Taysi, S., Tascan, A. S., Ugur, M. G., & Demir, M. (2019). Radicals, Oxidative/Nitrosative Stress and Preeclampsia. *Mini reviews in medicinal chemistry, 19*, 178–193. doi: 10.2174/1389557518666181015151350
10. Valko, M., Morris, H., & Cronin, M. T. (2005). Metals, toxicity and oxidative stress. *Current medicinal chemistry, 12*, 1161–1208. doi: 10.2174/0929867053764635
11. Dennery P. A. (2007). Effects of oxidative stress on embryonic development. Birth defects research. Part C, *Embryo today: reviews, 81*, 155–162. doi: 10.1002/bdrc.20098
12. BelAge. Available from: https://mx.prvademecum.com/medicamento/BelAge-13040/
13. Mendieta Zerón, H., García Solorio, V. J., Nava Díaz, P. M., Garduño Alanís, A., Santillán Benítez, J. G., Domínguez García, V., Escobar Briones, C., & Denova Gutiérrez, E. (2012). Hyperleptinemia as a prognostic factor for preeclampsia: a cohort study. *Acta medica (Hradec Kralove), 55*, 165–171. doi: 10.14712/18059694.2015.41.

14. Aouache, R., Biquard, L., Vaiman, D., & Miralles, F. (2018). Oxidative Stress in Preeclampsia and Placental Diseases. *International journal of molecular sciences, 19*, 1496. doi: 10.3390/ijms19051496

15. Tenório, M. B., Ferreira, R. C., Moura, F. A., Bueno, N. B., Goulart, M., & Oliveira, A. (2018). Oral antioxidant therapy for prevention and treatment of preeclampsia: Meta-analysis of randomized controlled trials. *Nutrition, metabolism, and cardiovascular diseases: NMCD, 28*, 865–876. doi: 10.1016/j.numecd.2018.06.002

16. Formoso, G., Baldassarre, M., Ginestra, F., Carlucci, M. A., Bucci, I., & Consoli, A. (2019). Inositol and antioxidant supplementation: Safety and efficacy in pregnancy. *Diabetes/metabolism research and reviews, 35*, e3154. doi: 10.1002/dmrr.3154

17. Xuan, R. R., Niu, T. T., & Chen, H. M. (2016). Astaxanthin blocks preeclampsia progression by suppressing oxidative stress and inflammation. *Molecular medicine reports, 14*, 2697–2704. doi: 10.3892/mmr.2016.5569

18. Kerley, R. N., McCarthy, C., Kell, D. B., & Kenny, L. C. (2018). The potential therapeutic effects of ergothioneine in pre-eclampsia. *Free radical biology & medicine, 117*, 145–157. doi: 10.1016/j.freeradbiomed.2017.12.030

19. Salles, A. M., Galvao, T. F., Silva, M. T., Motta, L. C., & Pereira, M. G. (2012). Antioxidants for preventing preeclampsia: a systematic review. *TheScientificWorldJournal, 2012*, 243476. doi: 10.1100/2012/243476

20. Rumiris, D., Purwosunu, Y., Wibowo, N., Farina, A., & Sekizawa, A. (2006). Lower rate of preeclampsia after antioxidant supplementation in pregnant women with low antioxidant status. *Hypertension in pregnancy, 25*, 241–253. doi: 10.1080/10641950600913016

21. Hofmeyr, G. J., Lawrie, T. A., Atallah, Á. N., & Torloni, M. R. (2018). Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. *The Cochrane database of systematic reviews, 10*, CD001059. doi: 10.1002/14651858.CD001059.pub5

22. Zuo, J., & Jiang, Z. (2020). Melatonin attenuates hypertension and oxidative stress in a rat model of L-NAME-induced gestational hypertension. *Vascular medicine (London, England), 25*, 295–301. doi: 10.1177/1358863X20919798

23. Sun, Y., Wang, C., Zhang, N., & Liu, F. (2021). Melatonin ameliorates hypertension in hypertensive pregnant mice and suppresses the hypertension-induced decrease in Ca2+-activated K+ channels in uterine arteries. *Hypertension research : official journal of the Japanese Society of Hypertension, 44*, 1079–1086. doi: 10.1038/s41440-021-00675-5

24. Mendieta Zerón, H., García Solorio, V. J., Nava Díaz, P. M., Garduño Alanís, A., Santillán Benítez, J. G., Domínguez García, V., Escobar Briones, C., & Denova Gutiérrez, E. (2012). Hyperleptinemia as a prognostic factor for preeclampsia: a cohort study. *Acta medica (Hradec Kralove), 55*(4), 165–171. doi: 10.14712/18059694.2015.41

25. Zerón, H. M., Flores, A. P., Chávez, A. A., Alanís, A. G., Ferreyra, M., Benítez, J. G., Castañeda, V. S., & García, M. V. (2013). Pregnancy Weight Gain Limitation by a Supervised Nutritional Program Influences Placental NF-κB/IKK Complex Expression and Oxidative Stress. *Oman medical journal, 28*, 167–172. doi: 10.5001/omj.2013.48