Myo-inositol in the treatment of airways diseases: a minireview

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ABSTRACT — Myo-Inositol (myo-Ins), key molecule participating in several intracellular signaling pathways and physiological processes, has been proven to modulate interleukin-6 (IL-6) levels in chronic inflammatory diseases and to possess endothelial protective properties. Moreover, myo-Ins promotes the maturation of pulmonary surfactant phospholipids, with beneficial effects in the treatment of premature infants with respiratory distress syndrome (RDS).

On these premises, myo-Ins has a potential application in the treatment of pulmonary diseases, and it could be successfully used to reduce the complications related to the SARS-CoV-2 pandemic event. Though information about the virus is still scarce, it is becoming evident that the Coronavirus infection triggers an interstitial pneumonia that quickly evolves into a severe RDS, associated with a thrombotic and vascular disease targeting endothelial cells throughout the body. These effects are most probably driven by a disastrous overreaction of the immune system, known as "cytokine storm", which interests not only lungs but also gut, kidneys, heart, and brain, with platelet-endothelial dysfunction and abnormally rapid life-threatening blood clotting. Given the pathophysiology of the SARS-CoV-2 disease (COVID-19), it could be worth investigating whether myo-Ins properties can mitigate the disease-related complications in terms of surfactant production, modulation of inflammatory cytokines and endothelial protection.

KEYWORDS
IL-6, Myo-inositol, Respiratory distress syndrome, SARS-CoV-2, Surfactant.

INTRODUCTION

Lung diseases are growing causes of morbidity and mortality, especially after the sudden rise of deaths due to the pandemic explosion of the SARS-CoV2 infections.

Chronic obstructive pulmonary disease (COPD) is currently the 5th cause of death and is rising such that in the next years is expected to be the 4th most common cause of death worldwide. Other inflammatory lung diseases such as cystic fibrosis and interstitial lung disease are also frequently encountered and are characterized by outcomes such as death or poor quality of life.

All these lung diseases are characterized by periodic or chronic inflammatory processes that can promote oncogenic transformations, genetic and epigenetic changes in malignant cells and a pro-tumorigenic inflammatory microenvironment with release of cytokines.

Among these inflammatory cytokines, interleukin-6 (IL-6) has received greater attention because of its implication in a plethora of pathological conditions including chronic inflammation, metabolic disorders, tumor development, therapeutic resistance, and metastasis[1].

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INTERLEUKIN-6 IN RESPIRATORY INFLAMMATORY DISEASES

Recent experimental reports indicate that IL-6 plays a pathogenetic role in respiratory system diseases. Indeed, IL-6 levels were increased in the airway epithelial cells of asthmatic children[2] and in the exhaled air[3] and blood[4] of asthmatic or COPD adult patients.

Other studies have provided indirect evidence that IL-6 causes respiratory system resistance increments: an inverse correlation between IL-6 in the sputum and Forced Expiratory Volume in the 1st second (FEV1) has been found in asthmatic and COPD patients[5-7]. Moreover, increased IL-6 levels correlating with impaired lung function have been reported in asthmatic and obese patients[8]. These data are extremely interesting because they suggest that IL-6, and possibly other cytokines, play a causative role in determining impaired respiratory mechanics, typically observed in respiratory diseases such asthma and/or COPD.

Another common chronic disorder usually co-existing with asthma is the allergic rhinitis. Its clinical symptoms include sneezing, nasal congestion, and rhinorrhea; additionally, this disease affects the peripheral blood, bone marrow, and the lungs[9]. Several factors have been reported to play an important role in the pathogenesis of allergic rhinitis[10]. Disequilibrium in the Th1/Th2 immune response could cause selective eosinophil accumulation in the nasal mucosa and production of allergen-specific immunoglobulin. Interactions between allergen-specific immunoglobulins and inhaled allergens in the upper airway could also play an important role in promoting the inflammatory process of allergic rhinitis[9,11]. Moreover, a recent case-control study showed that IL-6 rs1800795 polymorphism was associated with an increased risk of allergic rhinitis[12]. These data were confirmed by another study that found the promotor variants in IL-6, rs1800795, to be the predisposing factor for allergic rhinitis[13].

PULMONARY SURFACTANT AS A LUNG BARRIER OF THE HOST

An important defensive mechanism that protects lungs from infectious diseases is the pulmonary surfactant that acts as a mechanic barrier.

Pulmonary surfactant is a lipoprotein complex that is synthesized and secreted by type II alveolar epithelial cells and the airway cells into the thin liquid layer that lines the alveolar epithelium. Once in the extracellular space, surfactant carries out two distinct functions. First, it reduces surface tension at the air-liquid interface of the lung[14]. Second, surfactant plays a role in host defense against infections and inflammatory processes. *In vitro*, surfactant proteins have been shown to stimulate the phagocytosis, chemotaxis, and production of reactive oxygen and to regulate cytokine release by immune cells[15].

Thus, considering its pivotal role, surfactant inactivation and/or deficiency have been associated with a variety of lung diseases including pneumonia, asthma, and RDS in both adults and infants.

Namely, infants born before the term show immature lungs, unable to synthesize adequate amounts of functional surfactant and, therefore, there is an increase in surface tension and alveolar collapse[16]. If not treated, such atelectasis causes an increased work of breathing, intrapulmonary shunting, ventilation-perfusion mismatch, hypoxia, and eventual respiratory failure[17,18].

Similarly, surfactant abnormalities have been reported in Adult Respiratory Distress Syndrome (ARDS), an acute respiratory failure with generalized lung involvement that carries a mortality rate of 50% or more, despite recent advances in respiratory care[19-21]. ARDS is a heterogeneous syndrome associated with sepsis, aspiration, toxins, emboli, circulatory collapse, and metabolic, neurogenic, or hematologic disorders; however, the resulting abnormalities in lung function are similar[22,23]. Ashbaugh et al[24] have suggested that the surfactant system in ARDS patients is damaged and presents abnormalities.

These abnormalities were represented by low lecithin/sphingomyelin (L/S) ratio (<2), and low phosphatidylglycerol content (1% or less of glycerophospholipids) in bronchoalveolar lavage, always associated with respiratory failure.

Hallman et al [25], showed that abnormal phospholipid content in the lavage was not due to plasma contamination but caused by an increased catabolism of phospholipids.

Indeed, in respiratory failure, the lipid-protein complexes from lung lavage were surface inactive, whereas those from healthy controls had surface properties like lung surfactant.

Lung phospholipids from adult patients with respiratory failure bears similarities with those from RDS newborns[25].

MYO-INOSITOL IMPROVES LUNG SURFACTANT PROPERTIES

Several studies demonstrated that myo-inositol (myo-Ins), a naturally occurring polyol widely involved in several critical physiological processes[26], promotes maturation of pulmonary surfactant phospholipids: phosphatidylcholine and phosphatidylinositol. Indeed, extracellular myo-Ins concentrations regulate the synthesis of type II pneumocytes[27].

Moreover, surfactant enriched in myo-Ins content is associated with significantly better mechanical properties of alveoli. Myo-Ins and its phosphate derivatives recruit organic osmolytes and water within the alveolar space and foster the reconstitution of a bio-film layer at the interface, thereby decreasing surface tension and antagonizing collapsing forces[25].

Additionally, inositol promotes a mechanical stabilization of cell shape, mostly by modulating cytoskeleton dynamics, thus enabling alveolar cells to counteract collapsing forces[28].

Mechanical effects displayed by myo-Ins make this compound essential in affording pulmonary protection against atelectasis processes in preterm infants[26].

Early reports indicated that breast milk, especially colostrum, has a high concentration of inositol[29-31], and several studies have been conducted in the last two decades on the supplementation of myo-Ins to premature infants with RDS.

Among the most important placebo-controlled trial conducted on this topic, Hallman et at[32] demonstrated that the administration of inositol to premature infants with RDS, receiving parenteral nutrition during the first week of life, is associated with increased survival without bronchopulmonary dysplasia and with a decreased incidence of retinopathy of prematurity. In preterm infants with RDS, a premature drop in serum inositol levels predicts a more severe course of the disease, while supplementation with inositol leads to rise in serum inositol concentration and improvement in the surfactant phospholipids[33].

Moreover, studies with animal models confirmed the relationship between inositol and pulmonary surfactant. Indeed, compositional changes in fetal rat lung surfactant correlated with changes in plasma inositol levels, and supplementation restored normal phospholipid profile in the deprived rat pups[27,34].

Although only few published trials for myo-Ins supplementation have been subjected to systematic review, a Cochrane study[35] deemed the quality of the reports as appropriate. Thus, myo-Ins supplementation significantly reduces short-term adverse neonatal outcomes and the incidence of bronchopulmonary dysplasia.

Therefore, the effectiveness of inositol in reducing the severity of RDS is consistent with experimental data indicating that myo-Ins serves as a substrate that enhances the synthesis and secretion of surfactant phospholipids in immature lung tissue [36].

On these premises, myo-Ins deserves relevant consideration as a dietary supplement for premature infants, especially those not receiving full human milk feeds.

Moreover, beside the use in newborn with RDS, myo-ins supplementation should also be considered for treating ARDS.

MYO-INOSITOL AS MODULATOR OF IL-6

Interestingly, myo-Ins decreases IL-6 levels in several experimental settings, due to an effect on the inositol-requiring enzyme 1 (IRE1)-X-box-binding protein 1 (XBP1) and on the signal transducer and activator of transcription 3 (STAT3) pathways[37-39]. Moreover, myo-inositol, showed a strong chemo preventive activity in KRAS driven-lung cancer model of $Ccsp^{Cre/+}$; $Kras^{LSL-G12D/+}$ (CC-LR) mice by reducing circulating IL-6 levels and by switching to anti-tumoral M1 macrophages. Proteomic and cytokine analyses revealed large reduction in IL-6 related pathways, including STAT3 phosphorylation[40].

Other studies have proven myo-Ins action in modulating IL-6 levels in chronic inflammatory diseases such as polycystic ovary syndrome (PCOS), obesity and metabolic syndrome[41-43].

A study conducted on an animal model of PCOS with insulin resistance (PCOS-IR), demonstrated that myo-Ins supplementation leads to a downregulation of IL-6 and influences the regulation of several other molecular pathways.

Moreover, inositol specifically down-regulates IL-6 and PI3K (a key factor in the transduction of IL-6 signal), as well as inflammatory parameters – like PGE and COX2 – downstream of PI3K activation in different diseases like cancer and polycystic Ovary Syndrome (PCOS)[44].

MYO-INOSITOL SAFETY, APPLICATION, AND WAYS OF ADMINISTRATION

Myo-ins safety in humans has been assessed by several trials in which inositol was given for prolonged periods (from 1 to 12 months) at doses ranging from 4 to 30 g/day. Mild side effects (mostly represented by nausea or diarrhea) were reported in a small fraction of subjects, only for doses up to 12 g/day[45]. Myo-ins is currently added to some infant milk powder at the percentage of 0.01%, as it has been recognized as safe when used in accordance with good manufacturing or feeding practice[46]. Intravenous infusion of Myo-Ins is already used in pulmonology for the therapy of respiratory tract affections, asthma and chronic obstructive pulmonary disease and for the treatment of RDS in premature babies[32].

COVID-19 COMPLICATIONS

Compelling evidence report that the clinical presentation of COVID-19 begins with an acute respiratory distress. The SARS-CoV-2 virus quickly moves from the lungs throughout the vascular network, reaching the gut, the kidneys, the heart, and the brain, with associated platelet-endothelial dysfunction and abnormally rapid life-threatening blood clotting[47]. Indeed, SARS-CoV-2 infection is emerging as a thrombotic and vascular disease targeting endothelial cells throughout the body, being particularly evident in patients with cardiometabolic comorbidities (e.g. hypertension) with associated endothelial dysfunction[48].

It is well known that endothelial dysfunctions and thrombotic events are characterized by a suppressed endothelial nitric oxide synthase (eNOS) with concomitant nitric oxide (NO) deficiency. While the endothelium of healthy vessels releases nitric oxide, a vasodilator and antithrombotic factor, such process is impaired in injured vessels, resulting in hypertension and thrombus formation[49,50]. Some clinicians proposed that the driving force of potentially fatal outcomes in COVID-19 patients is a detrimental overreaction of the immune system known as a "cytokine storm", an abnormal release of certain cytokines that causes immune cells to attack healthy tissues. A cytokine storm may lead to leaking of blood vessels, drop in blood pressure and formation of clots, followed by catastrophic organ failure [47]. Myo-Ins has been proven to have endothelial protective and restoring properties[51,52]. Recent studies conducted on a genetically hypertensive animal model obtained using heterozygous mice for disruption of the endothelial nitric oxide synthase (eNOS) gene, showed that inositols supplementation (myo-inositol to D-chiro-inositol ratio 40:1) significantly improved vascular function. Indeed, systolic blood pressure resulted reduced and endothelial function (relaxation and contraction) improved, followed by the decrease of radical oxidative species, the enhancement of eNOS and NO bioactivity[53-56]. Moreover, inositols enhanced the expression of inducible nitric oxide synthase (iNOS) in those animals who were lacking the eNOS gene, demonstrating also a compensatory effect in the NO pathway[57]. Therefore, mechanical effects displayed by myo-ins together with its protective role on endothelial function as well as the ability to modulate the pro-inflammatory cytokines (IL-6), make this compound promising in the mitigation of the SARS-CoV2 infection complications.

CONCLUSIONS

Myo-Ins is a key molecule of important intracellular signaling pathways, where it participates as component of complex derivatives or in its free form. Myo-Ins influences the surfactant production, the modulation of inflammation, by downregulating the IL-6 production and exerts an endothelium protective action. These properties make inositol a key player in several biological activities. Thus, myo-Ins supplementation should be studied as a possible "non-pharmacologic" therapeutic strategy in several inflammatory and metabolic diseases such as PCOS, diabetes, pulmonary infections, and even as pioneering strategy to reduce the acute symptoms of COVID-19 and its fatal complications.

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References

1. Scheller J, Rose-John S. Interleukin-6 and its receptor: from bench to bedside. Med Microbiol Immunol 2006; 195: 173-183.
2. Kicic A, Sutanto E, Stevens P, Knight D, Stick S. Intrinsic biochemical and functional differences in bronchial epithelial cells of children with asthma. Am J Respir Crit Care Med 2006; 174: 1110-1118.
3. Carpagnano G, Foschino Barbaro M, Resta O, Gramiccioni E, Valerio NV, Bracciale P, Valerio G. Exhaled markers in the monitoring of airways inflammation and its response to steroid's treatment in mild persistent asthma. Eur J Pharmacol 2005; 519: 175-181.
4. Higashimoto Y, Yamagata Y, Taya S, Iwata T, Okada M, Ishiguchi T, Sato H, Itoh H. Systemic inflammation in chronic obstructive pulmonary disease and asthma: similarities and differences. Respirology 2008; 13: 128-133.
5. Morjaria J, Babu K, Vijayanand P, Chauhan A, Davies D, Holgate S. Sputum IL-6 concentrations in severe asthma and its relationship with FEV1. Thorax 2011; 66: 537-545.
6. Grubek-Jaworska, H Paplinska, M Hermanowicz-Salamon J, Bialek-Gosk, K Dabrowska, M Grabczak, E DogamalaKulawik, J Stepien J, Chazan R. IL-6 and IL-13 in induced sputum of COPD and asthma patients: correlation with respiratory tests. Respiration 2012; 84: 101-107.
7. Eickmeier O, Huebner M, Herrmann E, Zissler U, Rosewich M, Baer PC, Buhl R, Schmitt-Grohé S, Zielen S, Schubert R. Sputum biomarker profiles in cystic fibrosis (CF) and chronic obstructive pulmonary disease (COPD) and association between pulmonary function. Cytokine 2010; 50: 152-157.
8. Rincon M, Irvin C. Role of IL-6 in asthma and other inflammatory pulmonary diseases. Int J Biol Sci 2012; 8: 1281-1290.
9. Dávila I, Mullol J, Ferrer M, Bartra J. Genetic aspects of allergic rhinitis. J Investig Allergol Clin Immunol 2009; 19: 25-31.
10. Pawankar R, Hayashi M, Yamanishi S, Igarashi T. The paradigm of cytokine networks in allergic airway inflammation. Curr Opin Allergy Clin Immunol 2015; 15: 41-48.
11. Huang H, Zeng Z, Zhang L, Liu R. The association of interleukin-16 gene polymorphisms with susceptibility of coronary artery disease. Clin Biochem 2013; 46: 241-244.
12. Zhao N, Liu H, Sun Y, Li Y. Role of interleukin-6 polymorphisms in the development of allergic rhinitis. Genet Mol Res 2016; 15: 1-6.
13. Nasiri R, Movahedi M, Amirzargar AA, Hirbod-Mobarakeh A, Farhadi E, Ansaripour B, Moradi B, Rezaei N. Association of interleukin 6 single nucleotide polymorphisms with allergic rhinitis. Int J Pediatr Otorhinolaryngol 2014; 78: 1426-1429.
14. Whitsett J, Nogee L, Weaver T, Horowitz A. Human surfactant protein B: structure, function, regulation, and genetic disease. Physiol Rev 1995; 75: 749-757.
15. Wright J. Immunomodulatory functions of surfactant. Physiol Rev 1997; 77: 931-962.
16. Kopelman AE, Mathew OP. Common Respiratory Disorders of the Newborn. Pediatr Rev 1995; 16: 209-217.
17. Fan E, Brodie D, Slutsky AS. Acute respiratory distress syndrome advances in diagnosis and treatment. JAMA 2018; 319: 698-710.

18. Matthay M, Zemans R. The acute respiratory distress syndrome: pathogenesis and treatment. Annu Rev Pathol 2011; 6: 147-163.
19. Petty T, Ashbaugh D. The adult respiratory distress syndrome. Clinical features, factors influencing prognosis and principles of management. Chest 1971; 60: 233-239.
20. Moore F, Lyons J, Pierce E, Morgan AP, Drinker PA, Macarthur JD, Darwin GJ. Posttraumatic Pulmonary Insufficiency. BJS 1970; 57: 1-82
21. Simmons D, Nash G, Brigham K, Tierney D. Adult respiratory distress syndrome. West J Med 1979; 130: 218-235.
22. Hopewell P, Murray J. The Adult Respiratory Distress Syndrome. In Respiratory Emergencies. Annu Rev Med 1976; 27: 343-356.
23. Moss G. The role of the central nervous system in shock: the centroneurogenic etiology of the respiratory distress syndrome. Crit Care Med 1974; 2: 181-185.
24. Ashbaugh D, Bigelow D, Petty T, Levine B. Acute Respiratory Distress in Adults. Lancet 1967; 2: 319-323.
25. Hallman M, Spragg R, Harrell J, Moser K, Gluck L. Evidence of Lung Surfactant Abnormality in Respiratory Failure. Study of Bronchoalveolar Lavage Phospholipids, Surface Activity, Phospholipase Activity, and Plasma Myoinositol. J Clin Invest 1982; 70: 673-683.
26. Bizzarri M, Fuso A, Dinicola S, Cucina A, Bevilacqua A. Pharmacodynamics and pharmacokinetics of inositol(s) in health and disease. Expert Opin Drug Metab Toxicol 2016; 12: 1181-1196.
27. Guarner V, Tordet C, Bourbon J. Effects of maternal protein-calorie malnutrition on the phospholipid composition of surfactant isolated from the fetal and neonatal rat lungs. Compensation by inositol and lipid supplementation. Pediatr Res 1992; 31: 629-635.
28. Gilmore A, Burridge K. Regulation of vinculin binding to talin and actin by phosphatidylinositol-4-5-bisphosphate. Nature 1996; 381: 531-535.
29. Jacobs H, Jobe A, Ikegami M, Glatz T, Jones S, Barajas L. Premature lambs rescued from respiratory failure with natural surfactant: clinical and biophysical correlates. Pediatr Res 1982; 16: 424-429.
30. Pereira G, Baker L, Egler J, Corcoran L, Chiavacci R. Serum myoinositol concentrations in premature infants fed human milk, formula for infants, and parenteral nutrition. Am J Clin Nutr 1990; 51: 589-593.
31. Bromberger P, Hallman M. Myoinositol in small preterm infants: relationship between intake and serum concentration . J Pediatr Gastroenterol Nutr 1986; 5: 455-458.
32. Hallman M, Bry K, Hoppu K, Lappi M, Pohjavuori M. Inositol Supplementation in Premature Infants With Respiratory Distress Syndrome. N Engl J Med 1992; 326: 1233-1239.
33. Hallman M, Saugst O, Porreco R, Epstein B, Gluck L. Role of myo-inositol in regulation of surfactant phospholipids in the newborn. Early Hum Dev 1985; 10: 245-254.
34. Egberts J, Noort W. Gestational age-dependent changes in plasma inositol levels and surfactant composition in the fetal rat. Pediatr Res 1986; 20: 24-27.
35. Howlett A, Ohlsson A, Plakkal N. Inositol in preterm infants at risk for or having respiratory distress syndrome. Cochrane Database Syst Rev 2015; 2: CD000366.
36. Anceschi MM, Petrelli A, Zaccardo G, Barbati A, Di Renzo GC, Cosmi EV, Hallman M. Inositol and glucocorticoid in the development of lung stability in male and female rabbit fetuses. Pediatr Res 1988; 24: 617-621.
37. Fang P, Xiang L, Huang S, Jin L, Zhou G., Zhuge L, Li J, Fan H, Zhou L, Pan C, Yi Zheng. IRE1α-XBP1 signaling pathway regulates IL-6 expression and promotes progression of hepatocellular carcinoma. Oncol Lett 2018; 16: 4729-4736.
38. Zhang B, Gao C, Li Y, Wang M. D-chiro-inositol enriched Fagopyrum tataricum (L.) Gaench extract alleviates mitochondrial malfunction and inhibits ER stress/JNK associated inflammation in the endothelium. J Ethnopharmacol 2018; 214: 83-89.
39. Laganà AS, Unfer V, Garzon S, Bizzarri M. Role of inositol to improve surfactant functions and reduce IL-6 levels: A potential adjuvant strategy for SARS-CoV-2 pneumonia? Med Hypotheses 2020; 144: 110262.
40. Unver N, Delgado O, Zeleke K, Cumpian A, Tang X, Caetano MS, Wang H, Katayama H, Yu H, Szabo E, Wistuba II, Moghaddam SJ, Hanash SM, Ostrin EJ. Reduced IL-6 levels and tumor-associated phospho-STAT3 are associated with reduced tumor development in a mouse model of lung cancer chemoprevention with myo-inositol. Int J Cancer 2018; 142: 1405-1417.
41. Piranlioglu R, Korkaya H, Hassan K. Dietary myo-inositol chemoprevents lung carcinogenesis via boosting immune system in Kras mouse model. J Thorac Dis 2019; 11: 632-635.
42. Zhang C. MicroRNomics: a newly emerging approach for disease biology. Physiol Genomics 2008; 33: 139-147.
43. Zhang Y, Li C, Zhang W, Zheng X, Chen X. Decreased Insulin Resistance by Myo-Inositol Is Associated with Suppressed Interleukin 6/Phospho-STAT3 Signaling in a Rat Polycystic Ovary Syndrome Model. J Med Food 2020; 23: 375-387.
44. Gustafson AM, Soldi R, Anderlind C, Scholand MB, Qian J, Zhang X, Cooper K, Walker D, McWilliams A, Liu G, Szabo E, Brody J, Massion PP, Lenburg ME, Lam S, Bild AH, Spira A. Airway PI3K pathway activation is an early and reversible event in lung cancer development. Sci Transl Med 2010; 2: 26ra25.
45. Papaleo E, Unfer V, Baillargeon J, Fusi F, Occhi F, De Santis L. Myo-inositol may improve oocyte quality in intracytoplasmic sperm injection cycles. A prospective, controlled, randomized trial. Fertil Steril 2009; 91: 1750-1754.
46. U.S. Food & Drug Administration. Food and drugs chapter I - Food and drug administration department of health and human services subchapter E - Animal drugs, feeds, and trlated products. Code of Federal Regulations Title 21.
47. Wadman M, Couzin-Frankel J, Kaiser J, Matacic C. How does coronavirus kill? Clinicians trace a ferocious rampage through the body, from brain to toes. Science.Published online 2020. doi:10.1126/science.abc3208.
48. Varga A, Flammer A, Steiger P, Haberecker M, Andermatt, R Zinkernagel A. Endothelial cell infection and endotheliitis in Covid-19. Lancet 2020; 395: 417-1418.
49. Tousoulis D, Kampoli A, Tentolouris C, Papageorgiou, N Stefanadis C. The role of nitric oxide on endothelial function. Curr Vasc Pharmacol 2012; 10: 4-18.
50. Green S. Covid-19 accelerates endothelial dysfunction and nitric oxide deficiency. Microbes Infect 2020; 22: 149-150.
51. Lin Q, Zhao LB, Jing R, Trexler C, Wang H, Li Y, Tang H, Huang F, Zhang F, Fang X, Liu J, Jia N, Chen J, Ouyang K. Inositol 1,4,5-Trisphosphate Receptors in Endothelial Cells Play an Essential Role in Vasodilation and Blood Pressure Regulation. J Am Heart Assoc 2019; 8: 1-12.
52. Kunjara S, McLean P, Rademacher L, Rademacher TW, Fascilla F, Bettocchi S, Scioscia M. Putative Key Role of Inositol Messengers in Endothelial Cells in Preeclampsia. Int J Endocrinol 2016; 2016: 7695648.
53. Menichini D, Longo M, Facchinetti F. Maternal interventions to improve offspring outcomes in rodent models of diet-induced obesity: a review. J Matern Neonatal Med 2019; 32: 2943-2949.
54. Ferrari F, Facchinetti F, Ontiveros AE, Roberts RP, Saade MM, Blackwell SC, Sibai BM, Refuerzo JS, Longo M. The effect of combined inositol supplementation on maternal metabolic profile in pregnancies complicated by metabolic syndrome and obesity. Am J Obstet Gynecol 2016; 215: 503.e1-8.
55. Longo M, Alrais M, Tamayo E, Ferrari F, Facchinetti F, Refuerzo JS, Blackwell SC, Sibai BM. Vascular and metabolic profiles in offspring born to pregnant mice with metabolic syndrome treated with inositols. Am J Obs Gynecol 2019; 220: e1-9.

56. Menichini D, Alrais M, Liu C, Xia Y, Blackwell SC, Facchinetti F, Sibai BM, Longo M. Maternal Supplementation of Inositols, Fucoxanthin, and Hydroxytyrosol in Pregnant Murine Models of Hypertension. Am J Hypertens 2020; 33: 652-659.

57. Longo M, Mani A, Lu F, Ferrari F, Facchinetti F, Refuerzo JS, Sibai BM, Blackwell SC. Investigating the mechanisms leading to improved metabolic profile by inositol in pregnancy complicated by metabolic syndrome. Am J Obs Gynecol 2017; 216: S319-S320.