Original Article

The Effect of Adding Vaginal Progesterone to Oral Omega-3 Fatty Acids on the Birth Weight of Constitutionally Small for Gestational Age Fetuses: A Randomized Clinical Trial

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ABSTRACT

Aim: To investigate the effectiveness of adding vaginal progesterone to oral omega-3 fatty acids on the birth weight of constitutionally small for gestational age fetuses (SGA).

Materials and Methods: The study was a randomized clinical trial conducted from May 2020 to June 2022 at Assiut Woman's Health Hospital, Egypt including pregnant women in singleton fetuses (26-28 weeks) whose pregnancy was associated with constitutionally SGA fetuses. The eligible women were randomized to either group I (oral omega-3 fatty acids group) or group II (vaginal progesterone plus oral omega-3 fatty acids group); given daily till delivery. The primary outcome was the mean birth weight (gm) at the time of delivery. The data were analyzed using an unpaired t-test and the Chi-square test.

Results: Eighty women were divided equally into two groups. There was a statistically significant increase in the mean birth weight (gm) at the time of delivery in group II in comparison to group I (1762.74 ± 80.06 vs. 1852.94 ± 71.71, receptively; *p=0.000*). The mean of uterine artery resistant index (RI) has a statistically significant decrease at 32 weeks and 36 weeks (*p value=0.000*) and the mean of umbilical artery RI has a statistically significant decrease at 36 weeks (*p value=0.001*) in group II.

Conclusion: Adding vaginal progesterone to oral omega-3 fatty acids is superior to oral omega-3 fatty acids alone in increasing the birth weight of constitutionally SGA fetuses when given from 26-28 weeks gestation till delivery. The improvement of the feto-maternal blood flow may be behind the treatment result.

Key Words: Doppler, omega-3 fatty acids, progesterone, SGA.

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INTRODUCTION

SGA fetuses are infants born with a birth weight less than the 10th centile[1]. Low birth weight (LBW) fetuses comprise both preterm births and SGA[2]. They are at great risk for perinatal morbidity and mortality[3]. Many causes are responsible for the development of SGA fetuses, however; in a few cases, the cause could not be detected[4].

Constitutionally small fetuses are fetuses whose growth is low at all gestational ages but otherwise healthy[5]. In contrast to pathologic intrauterine growth restriction (IUGR), the constitutionally small fetuses have normal umbilical and middle cerebral artery Doppler velocimetry and normal amniotic fluid volume[6]. Continued biophysical testing and delivery at 38-39 weeks are recommended for those fetuses[7].

The trials to increase the blood flow to the uterus and/or the fetus may improve the neonatal outcomes in SGA[8]. Despite the presence of many lines of treatment for SGA, most of these lines are lacking evidence of effectiveness in the literature and they are looking for prevention rather than treatment of SGA[9, 10].

The free radicals release during pregnancy impairs vascular endothelial function and subsequent vasoconstriction will occur[11]. Omega-3 fatty acids, as antioxidants, inhibit free radicals release; this leads to an increase in the blood flow to the uterus and placenta which may improve pregnancy outcomes[12]. The effectiveness of omega-3 fatty acids on the birth weight of IUGR was studied before with promising results[9].

Progesterone is a smooth muscle relaxant; it has a vasodilator effect on the blood vessels[13]. It causes vasodilation of the placental vessels with maintaining low flow resistance and adequate blood flow in the placental circulation[14]. Vaginal progesterone is associated with vascular relaxation and increased blood flow in the uterine arteries more than other types of progesterone[15].

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From the above evidence; we think that vaginal progesterone may have a beneficial effect on constitutionally SGA fetuses if they were added to omega-3 fatty acids. So our study aimed to compare the effectiveness of oral omega-3 fatty acids versus vaginal progesterone plus omega-3 fatty acids on the birth weight of constitutionally SGA fetuses. To our knowledge, no randomized clinical trials have addressed this combination before.

PATIENTS AND METHODS

The study was a single-center, open randomized, parallel, and registered clinical trial (Clinical trial.gov-NCT0416198). It was conducted from 1st of May 2020 to 1st of June 2022 at Assiut Woman's Health Hospital, Egypt included women who attended for antenatal care and were referred as SGA. The study was approved by Assiut Medical School Ethical Review Board (IRB54256).

Eligible participants

Women aged 20–35 years who were pregnant in singleton fetus from 26-28 weeks and whose pregnancy was complicated with SGA fetus were included. SGA referred to an estimated fetal weight (EFW) or abdominal circumference (AC) that is <10th centile with no pathology present[16]. Those women had BMI from 20-30 kg/m^2, with normal Doppler indices in uterine and umbilical arteries at the time of recruitment[17, 18].

However; women with EFW or AC below the 5th percentile, had any risk factors for IUGR[16], multiple pregnancies, low amniotic fluid volume or premature pre-labor rupture of membranes, antepartum hemorrhage, fetal congenital anomalies, any contraindications for vaginal progesterone or oral omega-3 fatty acids or refused to participate were excluded.

Intervention:

The eligibility of the participants was assessed at the screening phase of the study. After obtaining informed consent, the demographic and obstetric data were collected. Gestational age was established by reviewing the reliable 1st day of the last menstrual period or having an ultrasound assessment of the crown–rump in the 1st trimester. General and physical examinations were also done.

All ultrasound examinations were done by a single sonographer with more than 5 years' experience (MKA) using Medison X8, USA machine at Assiut Advanced Fetal Medicine Unit (AFCU). The fetal weight was calculated based on sonographic measurements of the fetal head circumference, bi-parietal diameter, AC, and femur length according to the Hadlock-4 formula[19].

The uterine artery Doppler blood flow was measured in the main trunk of both right and left uterine arteries, 2– 3 cm medial to the anterior superior iliac spine while umbilical artery Doppler blood flow was measured at a free loop of the umbilical cord. The resistant index (RI) was calculated when at least three similar consecutive waves were seen[9]. The mean of both uterine arteries was taken.

A blocked randomization was done using https://www.sealedenvelope.com and a table of random numbers with allocation concealment was generated. The participants were allocated to either group I (Oral omega-3 fatty acids group); women in this group received oral omega-3 capsule (Omega 3 plus, SEDICO, Egypt); while women in group II (vaginal progesterone plus oral omega-3 group) received vaginal progesterone (Prontogest 400 mg vaginal suppository, Marcyrl Pharmaceutical Industries, Egypt) and oral omega-3 once daily started at 26-28 weeks till delivery.

Follow-up visits:

The participants were asked to come for follow-up at the Antenatal Care Clinic every two weeks till delivery. At each visit; the women were asked about the fetal movements. Adherence to the treatment was achieved by asking the women to get back the empty packs and carefully revise them. The reported side effects of the oral omega-3 and vaginal progesterone were also recorded. Ultrasonographic assessment of fetal weight, amniotic fluid volume, and Doppler blood flow in both uterine and umbilical arteries were assessed at 32 weeks and 36 weeks. CTG was done for women after 32 weeks if decreased fetal movement was present. A single course of corticosteroid was given between 34 0/7 weeks and 36 6/7 weeks.

Study outcomes

The primary outcome was the mean birth weight (gm) in both groups. While the secondary outcomes included the changes in the RI in the uterine and umbilical arteries, time and mode of delivery, neonatal outcomes, and the possible side effects of the oral omega-3 and vaginal progesterone.

Final participant status

At the end of the study, the patients were classified into completed the study or lost for follow-up. Women who opted to stop the treatment during follow-up visits were excluded.

Sample size:

The sample size calculation was based on the primary outcome (The difference in the mean birth weight). To estimate the required sample size; we calculated the mean birth weight (gm) in both groups in the first 10 women. We found that the mean birth weight in group I was 1900± 240 gm and the figure of group II was 2100 ± 235 gm. Using two-sided chi-square ($\chi 2$) test with α of 0.05, a total sample

size of at least 80 patients (40 in each arm) will have 95% power assuming a rate of loss for follow-up of 10%(Epi-info™, CDC, USA).

Statistical analysis:

The data was collected and analyzed by the Statistical Package for Social Science (SPSS Inc., Chicago, version 21). Comparisons between the groups were done using an unpaired t-test to compare the mean values in scale variables. Categorical data were shown by number or percentage. For dichotomous variables, chi-square was used to estimate the significance value. The *p-value <0.05* was considered statistically significant.

RESULTS

Ninety-two women were counseled for participation, however; 12 women were excluded from the study during the screening phase. Eighty women consented to participate and were divided equally into two groups (40 women in each group). However, 5 women in the group I and 6 women in group II were excluded during follow-up visits. So; 35 women in the group I and 34 women in group II were finally analyzed (Figure 1).

Both groups were similar in the socio-demographic and obstetrics data without statistically significant differences (Table 1). Table 2 shows that the estimated fetal weight was comparable in both groups at 26-28 weeks (*p value= 0.733*) and 32 weeks (*p value= 0.424*) while there was a statistically significant difference between groups at 36 weeks (1496.29±66.3 gm Vs.1556.97±62 gm, respectively; *p value=0.000*) (Table 2). In addition; the mean of uterine artery RI in both groups has no statistically significant difference at 26-28 weeks (*p value= 0.982*) while there was a statistically significant difference between groups at 32 weeks and 36 weeks (*p value=0.000*) (Table 2). Moreover; the mean of umbilical artery RI in both groups hasn't a statistically significant difference at 26-28 weeks (*p value= 0.267*) and 32 weeks (*p value= 0.321*) while there was a statistically significant difference between groups at 36 weeks (*p value=0.001*) (Table 2). No statistically significant differences were noted between both groups regards the side effect of the treatment (*p> 0.05*) (Table 3).

Regards our primary outcome; there was a statistically significant difference between both groups in the mean birth weight at the time of delivery (1762.74 ± 80.06 vs. 1852.94 ± 71.71, respectively; *p=0.000*). No statistically significant difference was noted between groups in the mode of delivery (*p=0.528*), the gestational age at time of delivery (*p=0.502*), the number of term/preterm fetuses (*p=0.224*), neonatal sex (*p= 0.722*), Apgar score of more than 7 (*p=0.555*), number of babies who were admitted to NICU (*p=0.865*) and neonatal NICU stay (*p=0.379*), and neonatal mortality at NICU (*p=0.315*) (Table 4).

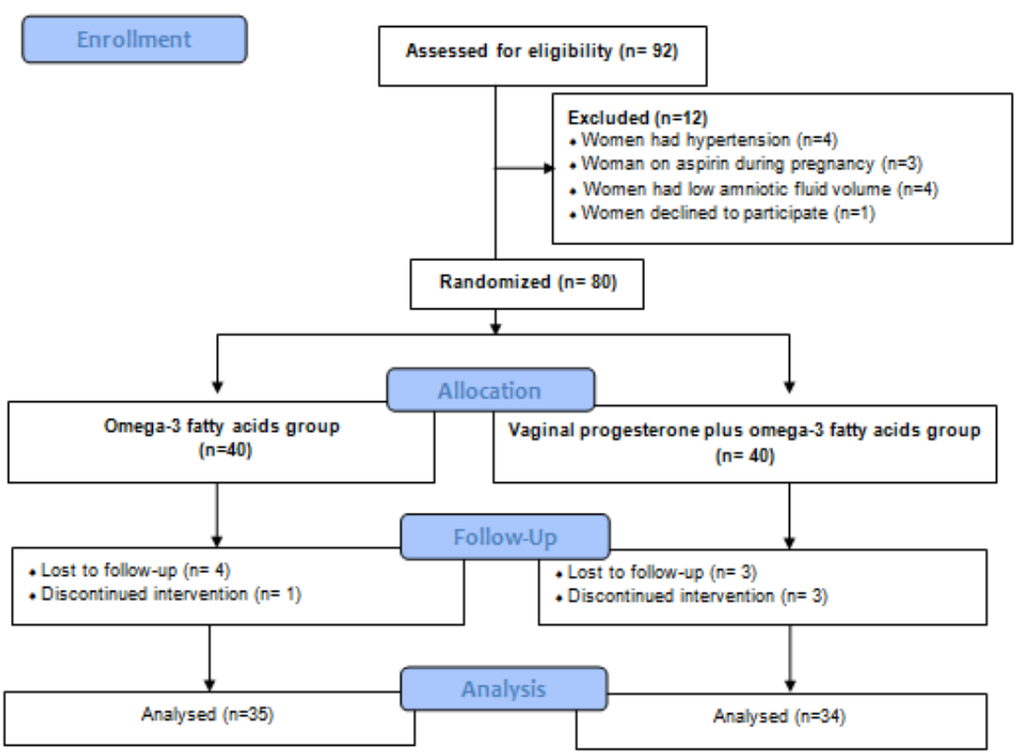

Fig. 1: Flow chart of the participants in the study

Table 1: Demographic and obstetric data of women in the study

	Group I (n= 40)	Group II (n= 40)	*P-value*
Age (years), mean ± SD	27.02 ± 5.40	27.97 ± 4.76	*0.407*
Residence, n (%)			
Urban	17 (42.5)	22 (55.0)	*0.263*
Rural	23 (57.5)	18 (45.0)	
Education, n (%)			
Illiterate	12 (30.0)	15 (37.5)	*0.644*
Basic	18 (45.0)	14 (35.0)	
Secondary or more	10 (25.0)	11 (27.5)	
Employment, n (%)	21 (52.5)	17 (42.5)	*0.370*
BMI (kg/m^2), mean ± SD	24.92 ± 2.87	25.07 ± 3.18	*0.826*
Parity, n (%)			
Primigravida	8 (20.0)	7(17.5)	
Para 1	13 (32.5)	12(30.0)	*0.841*
2-3	14 (35.0)	13(32.5)	
More than 3	5 (12.5)	8(20.0)	
History of previous abortion, n (%)	5(15.6)	7(21.2)	*0.562*
Mode of last delivery, n (%)			
VD	15(46.9)	18(54.5)	*0.536*
CS	17(53.1)	15(45.5)	
Number of living children, n (%)			
1	11 (34.4)	12 (36.4)	
2-3	17 (53.1)	13 (39.4)	*0.388*
More than 3	4 (12.5)	8 (24.2)	
Duration from the last pregnancy (years), median (Range)	2.7 (0.75-4.7)	3.0 (0.75-4.5)	*0.198*
Gestational age at time of recruitment (weeks), mean ± SD	26.85 ± 0.59	26.84 ± 0.59	*0.910*

BMI body mass index, **CS** cesarean section, **kg/m^2** Kilogram per square millimeter, **n (%)** number and percentage, **SD** standard deviation, **VD** vaginal delivery

Table 2: Comparison of the estimated fetal weight and mean uterine and umbilical artery RI between groups throughout gestation

	Group I	Group II	*P-value*
Estimated fetal weight (gm)			
At 26-28 weeks, mean ± SD	784.2860.1±	788.7256.1±	*0.733*
32 weeks, mean ± SD	1159.7675.4±	1175.7094.0±	*0.424*
36 weeks, mean ± SD	1496.2966.3±	1556.9762.1±	*0.000**
Uterine RI †			
At 26-28 weeks, mean ± SD	0.54 ± 0.10	0.54 ± 0.09	*0.982*
32 weeks, mean ± SD	0.46 ± 0.09	0.36 ± 0.08	*0.000**
36 weeks, mean ± SD	0.38 ± 0.08	0.27 ± 0.05	*0.000**
Umbilical RI †			
At 26-28 weeks, mean ± SD	0.66 ± 0.05	0.65 ± 0.04	*0.267*
32 weeks, mean ± SD	0.57 ± 0.09	0.55 ± 0.07	*0.321*
36 weeks, mean ± SD	0.47 ± 0.10	0.40 ± 0.06	*0.001**

* Statistical significant difference ($P < 0.05$)

gm gram, **RI** resistant index, **SD** standard deviation

† The data are only for those women who completed the study period and did not include those who stopped treatment or those who were lost for follow up.

Table 3: The reported side effects in both groups

Side effects†	Group I		Group II		*P-value*
	No.	%	No.	%	
No side effect	20	50.0%	21	52.5%	*0.823*
Heartburn	8	20.0%	5	12.5%	*0.363*
Nausea or vomiting	10	25.0%	5	12.5%	*0.152*
Diarrhea	6	15.0%	7	17.5%	*0.762*
Headache	8	20.0%	4	10.0%	*0.210*
Diarrhea	6	15.0%	7	17.5%	*0.762*
Constipation	0	0.0%	4	10.0%	*0.116*
Unusual vaginal bleeding	0	0.0%	4	10.0%	*0.116*
Skin rash	0	0.0%	2	5.0%	*0.494*

n (%) number and percentage
† The data are only for those women who completed the study period and did not include those who stopped treatment or those who were lost for follow up.

Table 4: Maternal and fetal outcomes in the present study

	Group I (n= 35)	Group II (n= 34)	*P-value*
Birth weight (gm), mean ± SD	1762.74 ± 80.06	1852.94 ± 71.71	*0.000**
Mode of delivery, n (%)			
VD after spontaneous onset of labor	7 (20.0)	9 (26.5)	
VD after induction of labor	5 (14.3)	8 (23.5)	
Planned CS	17 (48.6)	14 (41.2)	*0.528*
CS for fetal distress after induction	6 (17.1)	3 (8.8)	
Gestational age at time delivery (weeks), mean ± SD	37.69 ± 0.79	37.81 ± 0.76	*0.502*
Number of term/preterm, n (%)			
Term	27 (77.1)	30 (88.2)	*0.224*
Preterm	8 (22.9)	4 (11.8)	
Neonatal sex, n (%)			
Male	16 (45.7)	17 (50.0)	*0.722*
Female	19 (54.3)	17 (50.0)	
Apgar score more than 7, n (%)	22 (62.9)	19 (55.9)	*0.555*
Admission to NICU, n (%)	12 (34.3)	11 (32.4)	*0.865*
Neonatal NICU stay (days), median (Range)	4.0 (1.0-7.0)	3.0 (2.0-5.0)	*0.379*
Neonatal morality at NICU, n (%)	3 (25.0)	1 (9.1)	*0.315*

* Statistical significant difference (*P < 0.05*)
CS cesarean section, **gm** gram, **n (%)** number and percentage, **NICU** neonatal intensive care unit, **SD** standard deviation, **VD** vaginal delivery

DISCUSSION

To our knowledge, this is the first RCT addressing the effect of combining vaginal progesterone with oral omega-3 fatty acids on the birth weight of constitutionally SGA fetuses. The present work demonstrated that adding vaginal progesterone to oral omega-3 fatty acids was effective in increasing the birth weight more than oral omega-3 alone when given from 26-28 weeks to delivery. In addition; the increased rate of blood flow in the uterine and umbilical arteries was more prominent with this combination. Despite a significant difference in the birth weight; the maternal and neonatal outcomes were comparable in both groups.

In this study; we found that the birth weight was significantly increased when progesterone was added to omega-3 fatty acids from 26-28 weeks gestation till delivery (1762.74 ± 80.06 gm vs.1852.94 ± 71.71 gm; *p=0.000*). The progesterone and omega-3 seem to increase the vasodilation effect, so more improvement in the birth weight has occurred.

Olsen *et al*. in an old study found that birth weight was significantly higher in women with omega-3 fatty acids consumed in the form of fish[20]. Three years later, he concluded again that the weight and length of the newborn increased with the frequency of seafood dinner meal consumption[21]. Smuts CM *et al*. concluded that the consumption of omega-3 fatty acids in the form of eggs from 24-28 weeks until delivery increased birth weight significantly[22]. Moreover; Rogers *et al*. supported the hypothesis that the intake of omega-3 in the form of fish during pregnancy may increase fetal growth rate[23].

Prenatal omega-3 supplementation in primigravida may result in increased birth size. This fact was reported by Ramakrishnan *et al*. in 2010[24]. Cohen *et al*. study showed that the maternal intake of omega-3 fatty acids during the second trimester of pregnancy was associated with greater fetal growth[25]. Brantsæter *et al*. noticed that seafood intake was positively associated with birth weight[26]. Carlson *et al*. in 2013 found that a supplement of omega-3 fatty acids in the last half of gestation resulted in greater infant size[27]. Giorlandino *et al*. addressed the effect of vaginal omega-3 fatty acid on pregnant women who were at risk for preterm delivery[28]. Again; a systematic review concluded that the birth weight is higher with omega-3 fatty acids supplementation during pregnancy[29].

Regardless of the heterogeneity of the women in previous studies, different routes and sources, different starting and stoppage times of omega-3 supplementation during pregnancy; these studies proved the favorable results of omega-3 fatty acids on the birth weight. So, based on these studies; we think that omega-3 fatty acids can also increase the birth weight in SGA fetuses that are small and healthy.

However; Olsen *et al*. 1992 denied any beneficial effect of omega-3 in increasing birth weight[30]. They started the supplementation in the third trimester; this may be behind their different results. Also, Szajewska H *et al*. did not find any evidence that omega-3 supplementation influenced the rate of low-birth-weight infants[31].

We are on the same track as Ali MK *et al*. who proved in their study that the use of omega-3 was effective in increasing fetal weight in SGA fetuses[9]. Although he included women with asymmetrically IUGR but our results are still in agreement with him.

However; Bulstra-Ramakers in his study addressed the effects of omega-3 fatty acids on the recurrence rate of IUGR but he failed to find any beneficial effect of omega-3 fatty acids[10]. Moreover; Onwude *et al*. concluded that there was no evidence for any useful effect of fish oil supplementation for women with birth weight < 3rd centile[32]. However; his study included pregnant women at high risk of developing pregnancy-induced hypertension or asymmetrical IUGR. Again; Saccone *et al*. also concluded in a systematic review that included three studies that the omega-3 had no role in the prevention of recurrent IUGR[33]. Finally; a Cochrane review states that there is little or no evidence of a beneficial effect of omega-3 fatty acids on SGA fetuses[29]. These mentioned studies addressed the effect of omega-3 fatty acids on pathologic IUGR but not all of them looked at SGA that are small and healthy. So we are still unique regards this issue and we have a different cohort.

In the present study; we found a significant decrease in the uterine artery RI in the vaginal progesterone plus omega-3 group at 30-32 weeks and 34-36 weeks. While the umbilical artery RI decreased significantly at 34-36 weeks only.

Ali MK *et al*. tested the effect of adding omega 3 to aspirin on fetal weight as well as feto-maternal blood flow in asymmetrical IUGR fetuses. He found a significant increase in the blood flow in both uterine and umbilical arteries[9]. So we agree with his results.

Zarean E *et al*. found that dydrogesterone reduced the resistance index of the uterine artery and middle cerebral and increased fetal weight[34]. In spite, we used different types and routes of progesterone and our cohorts were different; we are still on the same track with his findings.

Progesterone, especially vaginal form, can reverse the vasoconstriction process in the feto-placental arteries and improves fetal and placental weights in IUGR fetuses[15, 35, 36]. Also, Jamal A *et al*. found that the use of vaginal progesterone suppressed the resistance of the uterine artery[37]. In contrast; Maged AM *et al*. concluded that the administration of vaginal progesterone has no significant effects on the uterine artery, umbilical artery, and MCA Doppler indices[38]. But all participants, in his study, were at high risk for preterm labour. Çintesun E *et al*. failed to find any influence on uterine artery PI from vaginal micronized progesterone[39]. However, the earlier gestational age (11 + 0 to 13 + 6 weeks), in his study, may be behind this different result. Agra IK *et al*. did not find any influence of vaginal progesterone on uterine circulation but they included women with twin gestations[40]. Barda G *et al*. did not find any effect of vaginal progesterone on the umbilical artery or uterine arteries[41]. Women shared in his study were at higher risk for preterm labor and much less than a dose of vaginal progesterone (200 mg) was dose.

There are some interesting points that should be discussed in our study, firstly; this is the first RCT that addressed the effect of adding vaginal progesterone to oral omega-3 on SGA fetuses. This combination was not reported before. This paves the way for a new strategy for treatment. Secondly; the studying of the blood flow effect of the treatment on umbilical and uterine arteries supported

our results as they are considered as a director marker for feto-maternal blood flow improvement. Thirdly; the ultrasound examinations were performed by a single experienced investigator.

However, the present work had some limitations. There is no control group that we can compare our results with it. It was infeasible to blind study participants due to the nature of the treatment. The small sample size was available for the final analysis. Moreover; in our study, we assessed only uterine and umbilical arteries' blood flow; however we did not deal with other fetal blood vessels such as middle cerebral artery.

CONCLUSION

Adding vaginal progesterone to oral omega-3 fatty acids is effective in increasing birth weight in SGA fetuses that seem small and healthy more than oral omega-3 fatty acids alone when taken from 26 to 28 weeks gestation till delivery. The improvement of uterine and umbilical blood flow may be behind the treatment result.

CONFLICT OF INTEREST

There are no conflicts of interests.

REFERENCES

1. Odibo AO, Francis A, Cahill AG, Macones GA, Crane JP, Gardosi J. Association between pregnancy complications and small-for-gestational-age birth weight defined by customized fetal growth standard versus a population-based standard. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2011 Mar;24(3):411-7. PubMed PMID: 20698736. Epub 2010/08/12. eng.

2. Shibata M, Ogawa K, Kanazawa S, Kawasaki M, Morisaki N, Mito A, *et al*. Association of maternal birth weight with the risk of low birth weight and small-for-gestational-age in offspring: A prospective single-center cohort study. PloS one. 2021;16(5):e0251734. PubMed PMID: 33989347. Pubmed Central PMCID: 8121327.

3. Molina Giraldo S, Alfonso Ayala DA, Arreaza Graterol M, Perez Olivo JL, Solano Montero AF. Three-dimensional Doppler ultrasonography for the assessment of fetal liver vascularization in fetuses with intrauterine growth restriction. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 2019 Mar;144(3):260-4. PubMed PMID: 30447077.

4. Ali MK, Abbas AM, Yosef AH, Bahloul M. The effect of low-dose aspirin on fetal weight of idiopathic asymmetrically intrauterine growth restricted fetuses with abnormal umbilical artery Doppler indices: a randomized clinical trial. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2018 Oct;31(19):2611-6. PubMed PMID: 28670938.

5. Figueras F, Gratacos E. Update on the diagnosis and classification of fetal growth restriction and proposal of a stage-based management protocol. Fetal diagnosis and therapy. 2014;36(2):86-98. PubMed PMID: 24457811.

6. McCowan LM, Harding JE, Roberts AB, Barker SE, Ford C, Stewart AW. A pilot randomized controlled trial of two regimens of fetal surveillance for small-for-gestational-age fetuses with normal results of umbilical artery doppler velocimetry. American journal of obstetrics and gynecology. 2000 Jan;182(1 Pt 1):81-6. PubMed PMID: 10649160.

7. Galan HL. Timing delivery of the growth-restricted fetus. Seminars in perinatology. 2011 Oct;35(5):262-9. PubMed PMID: 21962625.

8. Kalinka J, Gottwald L, Nowakowski M, Lech W, Zdziennicki A, Laudanski T. [The impact of low-dose aspirin therapy on umbilical and middle cerebral artery blood flow in pregnancy complicated by idiopathic intrauterine growth restriction]. Ginekologia polska. 2004 Apr;75(4):254-60. PubMed PMID: 15181862. Ocena wplywu malych dawek kwasu acetylosalicylowego na przeplyw krwi w tetnicy pepowinowej i srodkowej mozgu w ciazy powiklanej idiopatyczna hipotrofia plodu.

9. Ali MK, Amin ME, Amin AF, Abd El Aal DEM. Evaluation of the effectiveness of low-dose aspirin and omega 3 in treatment of asymmetrically intrauterine growth restriction: A randomized clinical trial. European journal of obstetrics, gynecology, and reproductive biology. 2017 Mar;210:231-5. PubMed PMID: 28068596.

10. Bulstra-Ramakers MT, Huisjes HJ, Visser GH. The effects of 3g eicosapentaenoic acid daily on recurrence of intrauterine growth retardation and pregnancy induced hypertension. British journal of obstetrics and gynaecology. 1995 Feb;102(2):123-6. PubMed PMID: 7756203. Epub 1995/02/01. eng.

11. Watanabe K, Mori T, Iwasaki A, Kimura C, Matsushita H, Shinohara K, *et al*. Increased oxygen free radical production during pregnancy may impair vascular

reactivity in preeclamptic women. Hypertension research : official journal of the Japanese Society of Hypertension. 2013 Apr;36(4):356-60. PubMed PMID: 23324862. Epub 2013/01/18. eng.

12. Ismail AM, Ramadan MF, Ali MK, Abbas AM, El Saman AM, Makarem MH. A randomized controlled study of the efficacy of 4 weeks of supplementation with ω-3 polyunsaturated fatty acids in cases of unexplained oligohydramnios. Journal of perinatology : official journal of the California Perinatal Association. 2016 Nov;36(11):944-7. PubMed PMID: 27559716. Epub 2016/10/26. eng.

13. Al-Shboul OA, Mustafa AG, Omar AA, Al-Dwairi AN, Alqudah MA, Nazzal MS, *et al*. Effect of progesterone on nitric oxide/cyclic guanosine monophosphate signaling and contraction in gastric smooth muscle cells. Biomedical reports. 2018 Dec;9(6):511-6. PubMed PMID: 30546879. Pubmed Central PMCID: 6256236.

14. Borna S, Bandarian M, Abdollahi A, Bandarian F, Malek M. Maternal progesterone level in fetal growth restriction and its relationship with Doppler velocimetry indices. Iranian journal of radiology : a quarterly journal published by the Iranian Radiological Society. 2011 Mar;8(1):33-7. PubMed PMID: 23329914. Pubmed Central PMCID: 3522412.

15. DeFranco EA, DeArmond C, Hook JV. Progesterone administration for the prevention of preterm birth: effect on uterine blood flow dynamics. AJOG. 2015;214(1):SUPPLEMENT , S293-S4.

16. Gynaecologists. RCoOa. The Investigation and Management of the Small-for-Gestational-Age. . London: RCOG. 2014;Green-top Guideline No. 31. .

17. Ayoola OO, Bulus P, Loto OM, Idowu BM. Normogram of umbilical artery Doppler indices in singleton pregnancies in south-western Nigerian women. The journal of obstetrics and gynaecology research. 2016 Dec;42(12):1694-8. PubMed PMID: 27762476.

18. Bahlmann F, Fittschen M, Reinhard I, Wellek S, Steiner E. Reference values for blood flow velocity in the uterine artery in normal pregnancies from 18 weeks to 42 weeks of gestation calculated by automatic Doppler waveform analysis. Ultraschall in der Medizin. 2012 Jun;33(3):258-64. PubMed PMID: 22274906.

19. Unterscheider J, O'Donoghue K, Daly S, Geary MP, Kennelly MM, McAuliffe FM, *et al*. Fetal growth restriction and the risk of perinatal mortality-case studies from the multicentre PORTO study. BMC pregnancy and childbirth. 2014 Feb 11;14:63. PubMed PMID: 24517273. Pubmed Central PMCID: 3923738.

20. Olsen SF, Olsen J, Frische G. Does fish consumption during pregnancy increase fetal growth? A study of the size of the newborn, placental weight and gestational age in relation to fish consumption during pregnancy. International journal of epidemiology. 1990 Dec;19(4):971-7. PubMed PMID: 2084030. Epub 1990/12/01. eng.

21. Olsen SF, Grandjean P, Weihe P, Viderø T. Frequency of seafood intake in pregnancy as a determinant of birth weight: evidence for a dose dependent relationship. Journal of epidemiology and community health. 1993 Dec;47(6):436-40. PubMed PMID: 8120495. Pubmed Central PMCID: PMC1059854. Epub 1993/12/01. eng.

22. Smuts CM, Huang M, Mundy D, Plasse T, Major S, Carlson SE. A randomized trial of docosahexaenoic acid supplementation during the third trimester of pregnancy. Obstetrics and gynecology. 2003 Mar;101(3):469-79. PubMed PMID: 12636950.

23. Rogers I, Emmett P, Ness A, Golding J. Maternal fish intake in late pregnancy and the frequency of low birth weight and intrauterine growth retardation in a cohort of British infants. Journal of epidemiology and community health. 2004 Jun;58(6):486-92. PubMed PMID: 15143117. Pubmed Central PMCID: 1732783.

24. Ramakrishnan U, Stein AD, Parra-Cabrera S, Wang M, Imhoff-Kunsch B, Juárez-Márquez S, *et al*. Effects of docosahexaenoic acid supplementation during pregnancy on gestational age and size at birth: randomized, double-blind, placebo-controlled trial in Mexico. Food and nutrition bulletin. 2010 Jun;31(2 Suppl):S108-16. PubMed PMID: 20715595. Epub 2010/08/19. eng.

25. Cohen JF, Rifas-Shiman SL, Rimm EB, Oken E, Gillman MW. Maternal trans fatty acid intake and fetal growth. The American journal of clinical nutrition. 2011 Nov;94(5):1241-7. PubMed PMID: 21918217. Pubmed Central PMCID: 3192475.

26. Brantsaeter AL, Birgisdottir BE, Meltzer HM, Kvalem HE, Alexander J, Magnus P, *et al*. Maternal seafood consumption and infant birth weight, length and head circumference in the Norwegian Mother and Child Cohort Study. The British journal of nutrition. 2012 Feb;107(3):436-44. PubMed PMID: 21767447.

27. Carlson SE, Colombo J, Gajewski BJ, Gustafson KM, Mundy D, Yeast J, *et al*. DHA supplementation and

pregnancy outcomes. The American journal of clinical nutrition. 2013 Apr;97(4):808-15. PubMed PMID: 23426033. Pubmed Central PMCID: 3607655.

28. Giorlandino C, Giannarelli D. Effect of vaginally administered DHA fatty acids on pregnancy outcome in high risk pregnancies for preterm delivery: a double blinded randomised controlled trial. Journal of prenatal medicine. 2013 Jul;7(3):42-5. PubMed PMID: 24175017. Pubmed Central PMCID: PMC3808943. Epub 2013/11/01. eng.

29. Middleton P, Gomersall JC, Gould JF, Shepherd E, Olsen SF, Makrides M. Omega-3 fatty acid addition during pregnancy. The Cochrane database of systematic reviews. 2018 Nov 15;11:CD003402. PubMed PMID: 30480773. Pubmed Central PMCID: 6516961.

30. Olsen SF, Sørensen JD, Secher NJ, Hedegaard M, Henriksen TB, Hansen HS, *et al*. Randomised controlled trial of effect of fish-oil supplementation on pregnancy duration. Lancet (London, England). 1992 Apr 25;339(8800):1003-7. PubMed PMID: 1349049. Epub 1992/04/25. eng.

31. Szajewska H, Horvath A, Koletzko B. Effect of n-3 long-chain polyunsaturated fatty acid supplementation of women with low-risk pregnancies on pregnancy outcomes and growth measures at birth: a meta-analysis of randomized controlled trials. The American journal of clinical nutrition. 2006 Jun;83(6):1337-44. PubMed PMID: 16762945. Epub 2006/06/10. eng.

32. Onwude JL, Lilford RJ, Hjartardottir H, Staines A, Tuffnell D. A randomised double blind placebo controlled trial of fish oil in high risk pregnancy. British journal of obstetrics and gynaecology. 1995 Feb;102(2):95-100. PubMed PMID: 7756226. Epub 1995/02/01. eng.

33. Saccone G, Berghella V, Maruotti GM, Sarno L, Martinelli P. Omega-3 supplementation during pregnancy to prevent recurrent intrauterine growth restriction: systematic review and meta-analysis of randomized controlled trials. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2015 Dec;46(6):659-64. PubMed PMID: 26033362. Epub 2015/06/03. eng.

34. Zarean E, Mostajeran F, Dayani Z. Effect of Dydrogesterone on the Outcome of Idiopathic Intrauterine Growth Restriction: A Double-blind Clinical Trial Study. Advanced biomedical research. 2018;7:93. PubMed PMID: 30050881. Pubmed Central PMCID: PMC6036772. Epub 2018/07/28. eng.

35. Alawadhi M, Mouihate A, Kilarkaje N, Al-Bader M. Progesterone partially recovers placental glucose transporters in dexamethasone-induced intrauterine growth restriction. Reproductive BioMedicine Online. 2021 2021/10/29/.

36. Paonessa DJ, Shields AD, Howard BC, Gotkin JL, Deering SH, Hoeldtke NJ, *et al*. 17-Hydroxyprogesterone caproate reverses induced vasoconstriction of the fetoplacental arteries by the thromboxane mimetic U46619. American journal of obstetrics and gynecology. 2006 Oct;195(4):1011-4. PubMed PMID: 16846582. Epub 2006/07/19. eng.

37. Jamal A, Moshfeghi M, Molaei B, Moradi Y, Hashemi N. The effect of vaginal progesterone on Doppler findings in increased uterine artery resistance. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2021 Aug;34(16):2630-3. PubMed PMID: 31665939. Epub 2019/11/02. eng.

38. Maged AM, Shoab AY, Hussein EA, Alsawaf AH, Mahmoud DS, AbdAllah AA, *et al*. The Effect of Antenatal Vaginal Progesterone Administration on Uterine, Umbilical, and Fetal Middle Cerebral Artery Doppler Flow: A Cohort Study. American journal of perinatology. 2020 Apr;37(5):491-6. PubMed PMID: 30866028. Epub 2019/03/14. eng.

39. Çintesun E, İncesu Çintesun FN, Mammadova N, Çelik Ç. The influence of vaginal progesterone on Uterine Artery Pulsatility Index. Ginekologia polska. 2021 Mar 23. PubMed PMID: 33757153. Epub 2021/03/24. eng.

40. Agra IK, Brizot ML, Miyadahira MY, Carvalho MH, Francisco RP, Zugaib M. The effect of prenatally administered vaginal progesterone on uterine artery Doppler in asymptomatic twin pregnancies. European journal of obstetrics, gynecology, and reproductive biology. 2016 Oct;205:11-4. PubMed PMID: 27552173. Epub 2016/08/24. eng.

41. Barda G, Ben-Haroush A, Barkat J, Malinger G, Luria O, Golan A, *et al*. Effect of vaginal progesterone, administered to prevent preterm birth, on impedance to blood flow in fetal and uterine circulation. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2010 Dec;36(6):743-8. PubMed PMID: 20196070. Epub 2010/03/03. eng.