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The Effect of Omega 3 on Pregnancy Complicated by Asymmetrical IUGR

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ABSTRACT

Background: Omega-3 improves fetal wellbeing. New results suggest that maternal docosahexaenoic acid supplements can help to normalize adipose malfunction and enhance adiponectin-induced enhancements in metabolism functioning in fetuses with intrauterine growth restriction.

Aim of the work: This study is the first randomized controlled trials (RCT), to our knowledge, using the combination of omega-3 fatty acid and aspirin in the therapy of intra uterine growth restriction (IUGR).

Patients and methods: The research compared the effects of low dosage aspirin and low molecular weight heparin and low dosage aspirin and low molecular weight heparin with omega-3 on asymmetrical IUGR fetuses in a certified, single-center, open-randomized, parallel treatment clinical trial. At the Obstetrics and Gynecology Department of Al-Hussein University Hospital and the Obstetrics and Gynecology Department of Bolak Eldakror General Hospital in Giza, Egypt, 100 women who are pregnant (28–32 weeks) with IUGR participated in this study.

Results: The flow of blood in uterine arteries after treatment was significantly different in all parameters and systolic to diastolic blood flow ratio (S\D) before treatment for patients using aspirin + low molecular weight heparin than for women managed with aspirin + low molecular weight heparin plus omega3 fatty acid, the distribution of blood flow in uterine arteries shows no any statistically significant before treatment in resistance index (RI) and pulsatility index (PI) in the case of after treatment and S\D before treatment shows highly statistically significant.

Conclusion: The combination of aspirin and omega-3 fatty acid is an efficient therapy for asymmetrical IUGR. Study of the extended impact of omega-3 fatty acids on women with asymmetrical IUGR.

Keywords: *Intrauterine growth restriction; Omega 3; Aspirin.*

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INTRODUCTION

An estimated fetal weight (EFW) or abdominal circumference (AC) below the tenth percentile is defined as an IUGR, whereas an EFW or AC below the third percentile is considered a severe IUGR. It is estimated that 10–15% of women who are pregnant are affected by IUGR. Obstetricians and perinatologists must notice growth-restricted foetuses since they are linked to a high rate of perinatal morbidity and death. [1]

Antenatal diagnosis of IUGR decreases the fetal morbidity and mortality which complicate IUGR. Accurate dating is the most important step. Other important steps are identification of the risk factors, monitoring of the EFW and symphysis to fundus distance (SF). [2]

IUGR has early complications as increase rate of preterm labor, intrauterine fetal death, still birth, respiratory distress syndrome and entero-colitis. The late complications include increase the risk for hypertension, type 2 diabetes mellitus, neurodevelopmental disorders and renal diseases. [3]

Polyunsaturated fatty acids containing a double bond at the third carbon atom from the end of the carbon chain make up Omega 3. The carboxylic acid end that is regarded as the "start" of the chain, so "alpha," and the methyl end that is regarded as the "tail" of the chain, hence "omega," are the two ends of fatty acids. Omega-3 has two mechanisms for improving fetal health: First, during gestation and lactation, maternal and docosahexaenoic acid supplements normalize IUGR-induced alterations in adipose deposit and expression of visceral peroxisome proliferator activated receptor (PPAR). Second, maternal docosahexaenoic acid supplements raise serum adiponectin and also adiponectin and adiponectin receptor expression in adipose tissue. New research shows that maternal docosahexaenoic acid supplements normalize adipose malfunction and enhance adiponectin-induced enhancements in metabolic functioning in IUGR. [4]

We can diagnose with two dimensional (2 D) ultrasound and choose the best for management by Doppler ultrasound. Three dimensional (3D) ultrasound also used for anomaly scan. In our study we used 2 D ultrasound to diagnose IUGR and for follow up the EFW. [5] We also used Doppler to follow up the blood flow in the umbilical and uterine arteries. [6] Following diagnosis of IUGR, evaluation of the fetal wellbeing is the next step in its management which includes: fetal movement, Non stress test (NST), biophysical profile (BPP) and Doppler indices. [7]

Researchers mentioned many drugs which can be used in IUGR treatment as acetyl salicylic acid (ASA), heparin, sildenafil and others. Other researchers used vitamins and minerals as omega 3 fatty acid, zinc, magnesium, folic acid, iron, vit A and vit B. [8]

Our study is the first RCT, to our knowledge, using the combination of omega-3 fatty acid and aspirin in the management of IUGR.

PATIENTS AND METHODS

The research compared the effects of low dosage aspirin and low molecular weight heparin and low dosage aspirin and low molecular weight heparin plus omega-3 on asymmetrical IUGR fetuses in a registered, single-center, open-randomized, parallel treatment clinical trial. Patient recruitment was performed at Obstetrics and Gynecology Department Al- Hussein University hospital & Obstetrics and Gynecology Department Bolak Eldakror General Hospital in Giza, Egypt. Both treatment arms were followed up from the time or recruitment till delivery.

This is an open, parallel, randomized controlled trial that has been clinically registered and included 100 women who were pregnant (28–32 weeks) with IUGR at the Obstetrics and Gynecology Department of Al-Hussein University Hospital and the Obstetrics and Gynecology Department of Bolak Eldakror General Hospital in Giza, Egypt. They have been randomly assigned to one of two groups: aspirin and low molecular weight heparin or aspirin and low molecular weight heparin plus omega 3. Doppler blood flow variations in the uterine and umbilical arteries, birth weight, timing and manner of birth, and neonatal intensive care unit (NICU) admissions were among the outcomes. The paired and unpaired t-tests have been utilized to analyze the outcome factors.

Inclusion Criteria: Age: between 20 and 35 years old, pregnant between 28 and 32 weeks, singleton gestation, asymmetrical IUGR, and normal uterine and umbilical Doppler indicators at the recruitment time.

Exclusion Criteria: Women with hypertension, multiple gestations, early membrane rupture, abnormal Doppler indices in the shape of Doppler blood flow indices > 2 standard deviation, absent diastolic flow, and finally, reversed flow, congenital fetal deformity, gestation accompanied by antepartum bleeding, and marked reduction in the volume of amniotic fluid.

Primary Outcome Measures: Estimated fetal weight (gm).

Secondary Outcome Measures: Changes in Doppler blood flow indicators in both arteries of the uterus. The changes in Doppler blood flow indices in umbilical artery. Weight of the fetus at the time of birth (gm). The total number of newborns admitted to the NICU.

Statistical analysis:

To code, process, and analyze the obtained data, IBM SPSS (Statistical Package for Social Sciences) version 22 for Windows® was used (IBM SPSS Inc, Chicago, IL, USA).The Shapiro-Walk test has been performed to determine if the data has a normal distribution. Frequencies and relative percentages have been employed to represent qualitative data. To compare two or more groups of qualitative data, employ the Chi square test ($\chi 2$). The mean ± SD (standard deviation) has been employed to express quantitative data. An independent samples t-test has been performed to compare two independent groups of normally distributed data (parametric data). P values of < 0.05 have been considered significant.

RESULTS

	aspirin + low molecular weight heparin	aspirin + low molecular weight heparin plus omega3 fatty acid	P value	Statistically significant
Age				
Mean	27.18	27.5	0.7284	N. S
SD	4.3	4.86		
Minimum	20	20		
Maximum	35	35		
Prev. abortion				
0	38	36	0.831	N. S
1	7	6		
2	3	5		
3	2	3		

Table 1: The study population's age and previous abortion distribution

A total of 100 patients have been chosen for the tests. The average age was 27.2 years old, the lowest age was 20 years old and the highest age was 35 years old for groups treated with Aspirin, and in the case of groups treated with Aspirin plus omega 3 fatty acid, the average age was 27.5 years old, the lowest age was 20 years old and the highest age was 35 years old. The distribution of age groups shows no any statistically significant, Previous abortion show almost the same between treated groups with no any statistically significant as shown in table (1).

	aspirin + low molecular weight heparin		aspirin + low molecular weight heparin plus omega3 fatty acid		P value	Statistically significant
	Mean	SD	Mean	SD		
Estimated weight Before treatment	1205.72	42.6	1208.83	31.45	0.6793	N. S
Estimated weight After treatment	1957.02	118.21	2209.94	158.57	<0.0001	Sig.
Statistical test used: Tow sample T-test						
A p-value of ≤ 0.05 represents statistical significance (95% confidence interval).						

Table 2: Relation between (Estimated weight) before and after with different treated groups

The Estimated weight after treatment high increase in weight for patients used aspirin + low molecular weight heparin plus omega 3 fatty acid with about 250 gm than patients treated with Aspirin, the distribution of weight groups shows no any statistically significant before treatment and shows highly statistically significant after treatment of data as shown in table (2).

	aspirin + low molecular weight heparin		aspirin + low molecular weight heparin plus omega3 fatty acid		P value	Statistically significant
	Mean	SD	Mean	SD		
Blood flow in umbilical arteries After treatment						
S\D	4.01	0.24	3.97	0.25	0.4843	N. S
RI	0.79	0.02	0.74	0.03	<0.0001	Sig.
PI	1.29	0.061	1.3	0.077	0.5863	N. S
Blood flow in umbilical arteries Before treatment						
S\D	3.8	0.29	4	0.31	0.9008	N. S
RI	0.74	0.027	0.74	0.021	0.2482	N. S
PI	1.26	0.077	1.32	0.093	0.3074	N. S
Statistical test used: Tow sample T-test						
A p-value of ≤ 0.05 represents statistical significance (95% confidence interval).						

Table 3: Relation between (Blood flow in umbilical arteries) before and following with different treated groups

The Blood flow in umbilical arteries following therapy show significant different in RI for patients used aspirin + low molecular weight heparin than women managed with aspirin + low molecular weight heparin plus omega 3 fatty acid, the distribution of Blood flow in umbilical arteries shows no any statistically significant after and before treatment only in case of RI after treatment shows highly statistically significant of data as shown in table (3).

	aspirin + low molecular weight heparin		aspirin + low molecular weight heparin plus omega3 fatty acid		P value	Statistically significant
	Mean	SD	Mean	SD		
Blood flow in uterine arteries After treatment						
S\D	4	0.16	3.68	0.42	0.0063	Sig.
RI	0.76	0.02	0.69	0.023	<0.0001	Sig.
PI	1.3	0.059	1.17	0.11	<0.0001	Sig.
Blood flow in uterine arteries Before treatment						
S\D	3.88	0.3	3.73	0.41	0.0002	Sig.

RI	0.75	0.03	0.71	0.032	0.3084	N. S
PI	1.21	0.08	1.18	0.1	0.111	N. S
Statistical test used: Tow sample T-test						
A p-value of ≤ 0.05 represents statistical significance (95% confidence interval).						

Table 4: Relation between (Blood flow in uterine arteries) before and after with different treated groups

The Blood flow in uterine arteries after treatment significant different in all parameter and S\D before treatment for patients used aspirin + low molecular weight heparin than patients managed with aspirin + low molecular weight heparin plus omega3 fatty acid, the distribution of Blood flow in uterine arteries shows no any statistically significant before treatment in (RI and PI) in case of after treatment and S\D before treatment shows highly statistically significant of data as shown in table (4).

	aspirin + low molecular weight heparin				**P value**	**Statistically significant**
	Pre-treatment		Post-treatment			
	Mean	SD	Mean	SD		
Estimated weight	1205.72	42.6	1957.02	118.21	<0.0001	Sig.
Blood flow in umbilical arteries						
S\D	4.01	0.24	3.88	0.29	0.0158	Sig.
RI	0.79	0.02	0.75	0.027	<0.0001	Sig.
PI	1.29	0.061	1.26	0.077	0.0254	Sig.
Blood flow in uterine arteries						
S\D	4	0.16	4.02	0.31	0.6519	N. S
RI	0.76	0.96	0.74	0.02	0.3762	N. S
PI	1.3	0.059	1.21	0.078	<0.0001	Sig.
Statistical test used: Tow sample T-test						
p-value≤0.05 considered statistically significant (95% confidence interval).						

Table 5: Relation between aspirin + low molecular weight heparin treated group before and after treatment

The Estimated weight show significant different with increase with about 750 gm,The Blood flow in umbilical arteries show significant decrease in all parameter after treatment, The Blood flow in uterine arteries after treatment show significant decrease in PIafter treatment as shown in table (5).

	aspirin + low molecular weight heparin plus omega3 fatty acid				**P value**	**Statistically significant**
	Pre-treatment		Post-treatment			
	Mean	SD	Mean	SD		
Estimated weight	1208.83	31.45	2209.94	158.57	<0.0001	Sig.
Blood flow in umbilical arteries						
S\D	3.98	0.25	3.68	0.42	<0.0001	Sig.
RI	0.74	0.03	0.69	0.021	<0.0001	Sig.
PI	1.3	0.077	1.17	0.12	<0.0001	Sig.
Blood flow in uterine arteries						
S\D	4	0.31	3.73	0.41	0.0006	Sig.
RI	0.74	0.02	0.71	0.032	<0.0001	Sig.
PI	1.32	0.09	1.18	0.1	<0.0001	Sig.
Statistical test used: Tow sample T-test						
A p-value of ≤ 0.05 represents statistical significance (95% confidence interval).						

Table 6: Relation between aspirin + low molecular weight heparin plus omega3 fatty acid treated group before and

after treatment.

The Estimated weight show significant different with increase with about 1000 gm. The blood flow in the arteries of the umbilical shows a significant decrease in all parameters after treatment. The blood flow in the arteries of the uterine after treatment shows a significant decrease in PI after treatment as shown in table (6).

DISCUSSION

IUGR is a frequent obstetric issue that impacts 10–15% of all women who are pregnant. It might be detected throughout the antepartum or postpartum phase. Recognizing growth-limited fetuses is extremely important for obstetricians and perinatologists, as these fetuses are more likely to have stillbirths, birth hypoxia and neonatal complications.[9]

The reasons for asymmetrically IUGR vary, but the therapy comprises primarily of either terminating the gestation or remaining in the uterus and optimizing the flow of blood to the uterus and/or the fetus. When the flow of blood is boosted, oxygen and other important nutrients are delivered to the fetus more effectively.[10] Nevertheless, in IUGR pregnancies, maternal plasma essential fatty acids (EFAs) are efficiently converted into long chain polyunsaturated fatty acids (LCPUFAs), as their proportions either stayed stable, as in the instance of docosahexaenoic acid (DHA), or increased, as in the instance of archidonic acid (AA), when compared to those identified in the appropriate for gestational age (AGA) group. The ratio of fetal plasma LCPUFA metabolites AA and DHA to their precursors linoleic acid (LA) and alpha linoleic acid (ALA) has been considerably reduced in IUGR pregnancies compared to maternal plasma.[11]

A total of 100 patients have been chosen for testing in this study. The average age is 27.2 and the lowest age is 20 years, the highest age is 35 years for the group treated with aspirin, and in the case of the group treated with aspirin plus omega-3 fatty acid, the average age is 27.5 and the lowest age is 20 year and the highest age is 35 years, the distribution of age groups shows no any statistically significant, Previous abortion show almost the same between treated groups with no any statistically significant. Also, in this study The Estimated weight after treatment high increase in weight for patients used Aspirin plus omega3 fatty acid with about 250 gm than patients treated with Aspirin, the distribution of weight groups shows no any statistically significant before treatment and shows highly statistically significant after treatment.

Maged et al.[12] conducted the first study of aspirin in the therapy of IUGR and found that low dosages of aspirin (1.5 mg/kg) may lower the percentage of IUGR newborns while also increasing delivery weight. In spite of the fact that their research had a shorter therapy period (10 days) than ours, such findings put us on track (6 weeks). Nevertheless, in their follow-up visits, they relied solely on biometric measures of the fetus, whereas we employed Doppler blood flow evaluation in addition to biometric measures as a direct indicator for feto-maternal blood flow enhancement.[12]

According to Jacobsson et al.[13], aspirin has been explored as a preventative strategy for IUGR and has promising outcomes. A recent systematic evaluation, on the other hand, found that low-dose aspirin (LDA) has almost no effect on IUGR prophylaxis.

According to Roberge et al.[14], low birth weight (BW < 2500 g) represents an important indicator of infant morbidity and mortality. Much of the research in the literature has demonstrated the effectiveness of aspirin (50–150 mg) in preventing IUGR, particularly in hypertension mothers, as well as its involvement in enhancing foetal hemodynamics.

The study done by Keelan et al.[15] showed that both therapies were helpful in raising the weight of the fetus following six weeks of therapy, but that the rate of gain was larger when aspirin was mixed with omega 3 than when aspirin was used alone.

Several studies have shown that omega-3 fatty acids are effective in raising the weight of the fetus throughout normal gestation. In the case of IUGR, Ramakrishnan et al.[16] found that omega3 was helpful in preventing IUGR when administered from 18 weeks of pregnancy till birth.

When omega 3 was administered from week 33 of pregnancy until birth, Lazzarin et al.[17] discovered that it had no effect on the therapy of IUGR. As a result, our optimistic findings could be attributed to earlier omega-3 consumption (from 28-30 weeks) and a combination of omega-3 fatty acids and aspirin. Furthermore, we backed up our findings by looking at the flow of blood in the umbilical and uterine arteries, which were not included in Olsen's research.

In IUGR, co-supplementing aspirin with a total of 1000 mg omega-3 fatty acids per day from 28–30 weeks till birth improves fetal weight and utero-placental blood flow. Other studies, however, show that taking 3 grams of omega-3 fatty acids each day from 12 to 14 weeks of pregnancy until birth had no effect on IUGR incidence. [18]

Lower omega-3 poly unsaturated fatty acid (PUFA) levels have been linked to a number of pregnancy problems, involving intrauterine growth restriction (IUGR), gestational diabetes mellitus (GDM), and pre-eclampsia. Taking omega-3 PUFAs throughout gestation has been demonstrated to increase average gestational duration and reduce the chances of preterm delivery and reduced birth weight. [19]

In the end, based on the comparison done by Harrington et al.20, they found that the weight of newborns born from moms who took Omega + aspirin was higher (3,167.5 ± 95.4 g) than the weight of newborns born from moms who only took ASA (3,109.0 ± 48,094 g). The difference was not statistically significant (p = 0.85).

The most recent study, Ureyen et al. [21], is the only one to reveal Doppler blood flow alterations in umbilical arteries following LDA therapy in IUGR fetuses. However, they only included women having normal Doppler blood flow at the time of recruitment, proving that aspirin improves feto-placental blood flow.

Grab et al.[22] discovered that omega-3 PUFA supplements reduced fasting plasma glucose (FPG), insulin resistance, and C-reactive protein (CRP) levels in women with GDM but had no effect on pregnancy outcomes in a meta-analysis.

Furthermore, from 15 weeks of gestation until birth, pregnant women who took fish oil (around 323 mg/day, including approximately 100 mg DHA) or sunflower oil demonstrated slightly extended pregnancy duration in infants with greater umbilical cord plasma DHA in the DHA-supplemented group versus placebo. However, this discovery did not achieve statistical significance[23] Our findings indicate that maternal DHA supplementation can help to enhance the neurodevelopmental findings of IUGR newborns who are at high risk of having poor neurological findings. [24]

CONCLUSION

The combination of aspirin and omega 3 fatty acid is an efficient therapy for asymmetrical IUGR. Study of the extended impact of omega-3 fatty acids on women with asymmetrical IUGR.

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