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Full length article

Evaluation of the effectiveness of low-dose aspirin and omega 3 in treatment of asymmetrically intrauterine growth restriction: A randomized clinical trial

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ABSTRACT

Objective: To test the effect of aspirin and omega 3 on fetal weight as well as feto-maternal blood flow in asymmetrical intrauterine growth restriction (IUGR).
Study design: This study is a clinically registered (NCT02696577), open, parallel, randomized controlled trial, conducted at Assiut Woman's Health Hospital, Egypt including 80 pregnant women (28–30 weeks) with IUGR. They were randomized either to group I: aspirin or group II: aspirin plus omega 3. The primary outcome was the fetal weight after 6 weeks of treatment. Secondary outcomes included Doppler blood flow changes in both uterine and umbilical arteries, birth weight, time and method of delivery and admission to NICU. The outcome variables were analyzed using paired and unpaired *t*-test.
Results: The estimated fetal weight increased significant in group II more than group I ($p = 0.00$). The uterine and umbilical arteries blood flow increased significantly in group II ($p < 0.05$). The birth weight in group II was higher than that observed in group I ($p < 0.05$).
Conclusion: The using of aspirin with omega 3 is more effective than using aspirin only in increasing fetal weight and improving utero-placental blood flow in IUGR.

Introduction

Intrauterine growth restriction (IUGR) refers to a fetus that has failed to get a specific measures threshold by a specific gestational age [1]. Asymmetric type of IUGR is known by normal sized head and brain with smaller abdomen [2].

IUGR is a common obstetric problem which affects approximately 10–15% of pregnant women. It may be diagnosed at antepartum or postnatal period [3,4]. It is very serious for obstetricians as well as the perinatologists to recognize the growth restricted fetuses, because these fetuses are at greater risk of stillbirth, birth hypoxia and neonatal complications [5].

The causes of asymmetrically IUGR are varies greatly, however; the treatment mainly consists of either termination of pregnancy or staying in the uterus and improving blood flow to the uterus and/or the fetus. When blood flow is improved, the oxygen and other beneficial nutrients will deliver well to the fetus [6].

There are many lines of treatment have been emerged now for treatment of asymmetric type of IUGR like maternal rest and oxygenation, aspirin therapy, supplementation of zinc and fish oil. However; all mentioned lines of treatment lacking evidence of effectiveness in literature [7].

The role of low-dose aspirin therapy in management of IUGR is controversial. It has been used, in many studies, in prevention of IUGR especially in women at high risk of pre-eclampsia or obstetrical antiphospholipid syndrome [8].

Oxidative stress during pregnancy leads to free radicals release and subsequent disruption of the ability for the vasodilatation; thus, vasoconstriction may lead to decreased blood flow to the uterus and placenta resulting in IUGR [9].

Omega-3 fatty acids are antioxidants and important for normal growth and development. The women can get them through food like fish, some plants, and nut oils [10]. Omega-3 fatty acids such as EPA (eicosapentanoic acid) and DHA (docosahexanoic acid) are used by women to improve pregnancy outcomes, without any comprehensible recommendations. The omega-3 fatty acids have

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been studied also as preventive option for IUGR with relatively good results [11].

As mentioned before, most of studies in literature have reported the preventive effect of aspirin and omega 3 on IUGR with little information about its treatment roles. So the aim of our study is to address the effect of aspirin and omega-3 on fetal and birth weight as well as feto-maternal blood flow in asymmetrical IUGR cases.

To our knowledge, no randomized clinical trials have been conducted or registered, to compare the effect of aspirin and omega 3 on asymmetrically IUGR fetuses.

Materials and methods

The current study is a clinically retrospectively registered, open, parallel, randomized controlled trial (NCT02696577) comparing the effect of aspirin and aspirin plus omega 3 on pregnant women complicated with asymmetrical IUGR. The ethical review board of the Faculty of Medicine of the Assiut University approved the study. The participants were recruited from our Obstetrics Outpatients Clinics of the Woman's Health Hospital, Assiut University, Egypt. It was carried out in the period between the first of March 2015 and the first of February 2016. This trial was designed and reported according to the revised recommendations of ClinicalTrials.gov for improving the quality of reporting randomized clinical trials (RCTs).

Eligible participants

All pregnant women (28–30 weeks), whose pregnancy was complicated with asymmetrically IUGR were invited to participate in our study. Asymmetrically IUGR diagnosed by 2D trans-abdominal US when the abdominal circumference (AC) reduced out of proportion to other fetal biometric parameters (biparietal diameter and head circumference) and is below the 10th percentile [1], so there was increased HC:AC ratio [12]. We included in our study women aged 20–35 years with normal Doppler indices in uterine and umbilical arteries at time of recruitment (the normal value of S/D ratio is from 2.5 to 3.5; RI is from 0.60 to 0.75 and of PI is from 0.96 to 1.270, respectively) [13]. Informed consent was obtained for participation after discussing the nature of the study including the possible side effects of both aspirin and omega 3.

The participated women were entered the screening phase of the study. This phase included history taking (about parity and gestational age which confirmed by revising the given reliable 1st day of last menstrual period or having 1st trimester US defining gestational age). All risks factors for IUGR were revised with the recruited women [14]. Clinical examination including BMI and blood pressure were also assessed.

We excluded women, aged $\leq$20 and $\geq$35 years, women with any hypertensive disorder, diabetes mellitus, smokers, multiple gestations, low amniotic fluid volume, premature pre-labor rupture of membranes, antepartum hemorrhage and fetal congenital anomalies. We also excluded women had abnormal Doppler indices at the time of recruitment in the form of Doppler indices >2 SDs, absent diastolic flow or reversed flow.

Randomization

Randomization was done by computer-generated random table. Eligible women who gave their informed consent were randomized to either group I: low dose aspirin group or group II: low dose aspirin plus omega 3 group. Allocation concealment was done using serially numbered closed opaque envelopes. Each envelope was labeled with a serial number and had a card noting the intervention type. Allocation never changed after opening the closed envelopes.

Intervention

The eligible women were allocated to either group I (aspirin group); received (Aspirin 81, European Egyptian pharmaceuticals) once daily for 6 weeks and group II (low dose aspirin plus omega 3 group) received (Aspirin 81, European Egyptian pharmaceuticals) and Omega 3 (Omega 3 plus, SEDICO, Egypt); once daily for 6 weeks. The omega 3 plus capsule contains 1000 mg Fish Oil (contains Eicosapentaenoic acid (EPA) 13% & Docosahexaenoic acid (DHA) 9%) plus 100 mg Wheat Germ Oil (Linoleic acid 52–59%) as a natural source of Vitamin E. Participants were instructed to use the drug as prescribed.

Study outcomes

Primary outcome was the changes in fetal weight after 6 weeks of treatment. Secondary outcomes included Doppler blood flow changes in both uterine and umbilical arteries from before to 6 weeks after using aspirin and omega 3. Finally; birth weight, time and method of delivery and admission to NICU were also reported.

Follow-up schedule

Follow up schedule was arranged according to royal college of obstetrics and gynecology (RCOG) recommendations [1]. The participants were followed up every 2 weeks; at each visit, we were asking them about adequacy of fetal movement then they were subjected to 2 D obstetric ultrasound for fetal growth and Doppler blood flow study of both uterine and umbilical arteries.

The umbilical artery Doppler blood flow was measured at free loop of umbilical cord. The uterine artery Doppler blood flow was measured with patients in the recumbent position with slight left lateral tilt, using (Sonoline G60 S Ultrasound imaging system, Siemens, Germany); with a convex probe 3.5 MHz. The high pass filter was set at 125 Hz. The blood flow velocity waveform was studied in the main trunk of both right and left uterine arteries, 2–3 cm medial to the anterior superior iliac spine. The average value of systolic/diastolic ration (S/D), resistance index (RI) and pulsatility index (PI) was calculated when three similar consecutive waves were obtained.

Final status of the participant

Finally, the patients were classified into completed follow up visits or lost for follow up. Treatment failure was defined as the need for delivery due to static fetal growth over 3 weeks or ominous Doppler indices in the form of absent end-diastolic blood flow or reversed flow.

Sample size

Sample size calculation was based on the primary outcome (improvement of estimated fetal weight). The previous non randomized study reported that aspirin improved the fetal weight from 17.9% to 42.9% [15]. Using two sided chi-square ($\chi 2$) test with α of 0.05, a total sample size of at least 68 patients (34 in each arm) will have 80% power detect a 25% difference assuming a rate of loss to follow-up of 10% (Epi-info^{TM}, CDC, USA).

Statistical analysis

The data were collected and entered into a Microsoft Access database and were analyzed using the Statistical Package for Social Science (SPSS Inc., Chicago, version 21). The demographic characteristics and baseline data were compared between the groups. The outcome variables were calculated using a paired *t*-test