Effects of oral ginkgo biloba extract on pregnancy complicated by asymmetrically intrauterine growth restriction: a double-blinded randomized placebo-controlled trial

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Abstract:

Objectives: to evaluate the effect of oral ginkgo biloba extract (GB)) on asymmetrical intrauterine growth restriction (IUGR).

Study Design: A randomized trial conducted at Assiut Women Health on 226 pregnant women with asymmetrical IUGR. The patients randomly received GB extract or placebo for 6 weeks. The main outcome measures were improvement in fetal weight and feto-maternal blood flow. The data were analyzed by Student's t- test and chi-squared tests.

Result: There was a significant increase in the estimated fetal weight in the GB group (3047+ 127 gm) when compared to the placebo group (2734+ 127 gm) (p=<0.001). Moreover; there were significant increases in feto-maternal blood flow in GB group compared to the placebo group.

Conclusions: GB extract improves placental functions, Doppler indices and fetal weight in pregnancies complicated with IUGR fetuses.

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Introduction

The use of herbal medicinal products is increasing enormously in recent years.[1] Many women are using them for menstrual problems, menopausal symptoms, mood disturbances and to strengthen their bones.[2] Most of these benefits are due to the flavonoids present in these products. These flavonoids have anticarcinogenic, antiviral, antioxidant and anti-inflammatory activities, as well as being used in the treatment of osteoporosis, menopausal symptoms and cardiovascular diseases.[3]

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Besides the benefits from the consumption of flavonoids, little is known about their safety and potentially harmful toxic effects, such as mutagenicity and genotoxicity which might occur if taken in large doses.[4]

GB is a flavonoid medicinal plant that has its origin in China, Korea and Japan where the fruit and leaves have been used as food and medicine for a long time.[5] The major flavonoids in the GB extract are kaempferol, quercetin and isorhamnetin whose metabolites were found in the blood and urine after oral administration.[6]

GB has not been reported in the evidence-based medicine literature as being either safe or contraindicated in pregnancy or lactation. A higher incidence of postpartum hemorrhage was reported in the literature when associated with a 3 months ingestion of GB extract.[7]

Due to its actions as an anti-inflammatory and antioxidant, GB has been largely used in the treatment of Alzheimer's disease, pre-menstrual syndrome, cerebrovascular insufficiency and peripheral arterial occlusive disease.[8] In folk medicine, GB is used as a vermifuge, to induce labor, for the treatment of bronchitis, chronic rhinitis, chilblains, arthritis and edema.[9]

Intrauterine growth restriction (IUGR) refers to a fetus that has failed to achieve a specific biometric or estimated weight threshold by a specific gestational age. Asymmetric IUGR is characterized by the head and brain being normal in size, but the abdomen is smaller. IUGR fetuses are at greater risk of stillbirth, birth hypoxia and neonatal complications.[10]

Although there are many causes of asymmetrical IUGR, the treatment consists of either termination of pregnancy or remaining in utero and improving blood flow to the uterus. When blood flow is improved, the oxygen and other nutrients will deliver well to the fetus.[11]

Many lines of treatment are available now for treatment of the asymmetric type of IUGR like maternal rest and oxygenation, aspirin therapy, supplementation of zinc and fish oil. However; all mentioned lines of treatment lack evidence of effectiveness in literature.[12]

Our hypothesis is that the use of GB extract may improve the uterine blood flow and subsequently improve the placental functions and fetal weight. So the aim of this study was to evaluate the effect of oral supplementation of GB extract on the fetal weight as well as on the feto-maternal blood flow in cases of asymmetrical IUGR.

To our knowledge, no randomized clinical trials have been conducted or registered, to test the effect of GB on fetal weight and Doppler blood flow in asymmetrical IUGR fetuses.

Materials and Methods

The current study is a clinically registered double blinded, parallel, randomized controlled trial (NCT02425436) compassing the effect of GB extract on pregnant women 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 Women's Health Hospital, Assiut

University, Egypt. It was carried out in the period between the first of May 2014 and the first of December 2015. This trial was designed and reported according to the revised recommendations of ClinicalTrials.gov for improving the quality of reporting RCTs.

Eligible participants

All pregnant women (28-30 weeks), whose pregnancy was complicated with asymmetrical IUGR were invited to participate in our study. Asymmetrical IUGR diagnosed by 2D transabdominal ultrasound (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, so there was increased HC:AC ratio.[11] We included in our study women aged 20-35 years with normal Doppler indices in uterine, umbilical and middle cerebral arteries at time of recruitment (the normal value of S/D ratio is from 2.5-3.5; RI is from 0.60-0.75 and of PI is from 0.96 -1.270, respectively).[12] Informed consent was obtained for participation after discussing the nature of the study including the possible side effects of the GB.

The recruited women entered the screening phase of the study. This phase included history taking (including parity and gestational age). All medical and surgical risks factors for IUGR were reviewed with the patient.[13] Clinical assessment of BMI, blood pressure and fundal level were also done.

We excluded women, aged ≤20 and ≥ 35 years, women with hypertension, diabetes mellitus, smokers, low amniotic fluid volume, premature pre-labor rupture of membranes (PPROM), antepartum hemorrhage and fetal congenital anomalies. We also excluded women with 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 the secretary of the Statistics Unit at Assiut University Hospital using a computer-generated random table. 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 remained unchanged after opening of the closed envelopes.

Intervention

The eligible women were allocated to either group I (GB group); which received GB extract (Tebonina Forte 40 mg, Epico, Egypt) two tablets per day for 6 weeks, while group II (placebo group) received two tablets of placebo per day for the same duration. The placebo tables had the same size, color, weight and shape of as the GB tablets, which were manufactured at the Faculty of Pharmacology, Assiut University, Egypt. Many studies had tested GB 120 to 240 mg daily in divided doses in non-pregnant women,[14] however; here we tested a minimal dose (80 mg) of GB during pregnancy.

Study outcomes

The primary outcome was the improvement of fetal weight after 6 weeks of GB use. Secondary outcomes

included Doppler blood flow changes in uterine, umbilical arteries and middle cerebral artery from before to 6 weeks after GB use.

Follow-up schedule

The follow up schedule was arranged according to Royal College of Obstetrics and Gynecology (RCOG) recommendations.[13] 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 a 2 D obstetric ultrasound for fetal growth and a Doppler blood flow study of the uterine, umbilical and middle cerebral artery.

Doppler blood flow changes in the umbilical artery were measured at free loop. Measurements of the uterine artery blood flow velocity waveforms were carried out in both uterine arteries. With patients in the recumbent position with a slight left lateral tilt, a device that combines B-mode-imaging and bi-directional pulsed colored Doppler technique with real time spectral analysis (Sonoline G60 S Ultrasound imaging system, Siemens, Germany), using a convex probe 3.5 MHz, was used. 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.

For measurement of the middle cerebral artery (MCA) blood flow, the fetal head was in the transverse plane and the color Doppler ultrasound was overlying the anterior wing of the sphenoid bone near the base of the skull with an angle that approximates zero degrees was achieved by moving the transducer on the maternal abdomen. The average value of systolic/ diastolic ration (S/D), resistance index (RI) and pulsatility index (PI) were calculated when three similar consecutive waves were obtained.[22]

Final status of the participant

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

Sample size

Sample size was calculated with assuming that power 90% and two sided C.I. 95%, so the needed sample size will be 113 in each arm with a total patients number is 226 (Epi-info™, Centers for Disease Control and Prevention, USA).

Statistical analysis

The data were entered on Microsoft Access database and analyzed using the Stat view by Apple. Comparisons between the groups were performed using Student's t-test to compare the mean values between groups in scale variables. However, chi-squared tests were used to compare the dichotomous and ordinal variables in the groups. For analysis, P-value < 0.05 was considered significant.

Results

Out of 300 patients with evidence of asymmetrical IUGR, 226 consented to participate. The main reasons for not consenting included that they were

either not willing to share in an RCT (60 patients) or had no reason for declining to participate (14 patients).

Consenting women were randomized into two groups: GB group or placebo group. At the end of the study, 3 patients (2.65%) were not included in the analysis in the GB group and 7 patients (6.19%) were not included in placebo group; all of them were lost for follow-up. Therefore, their data were excluded from the final analysis and we included the data of only 110 patients in GB group and 106 patients in placebo group (Figure 1).

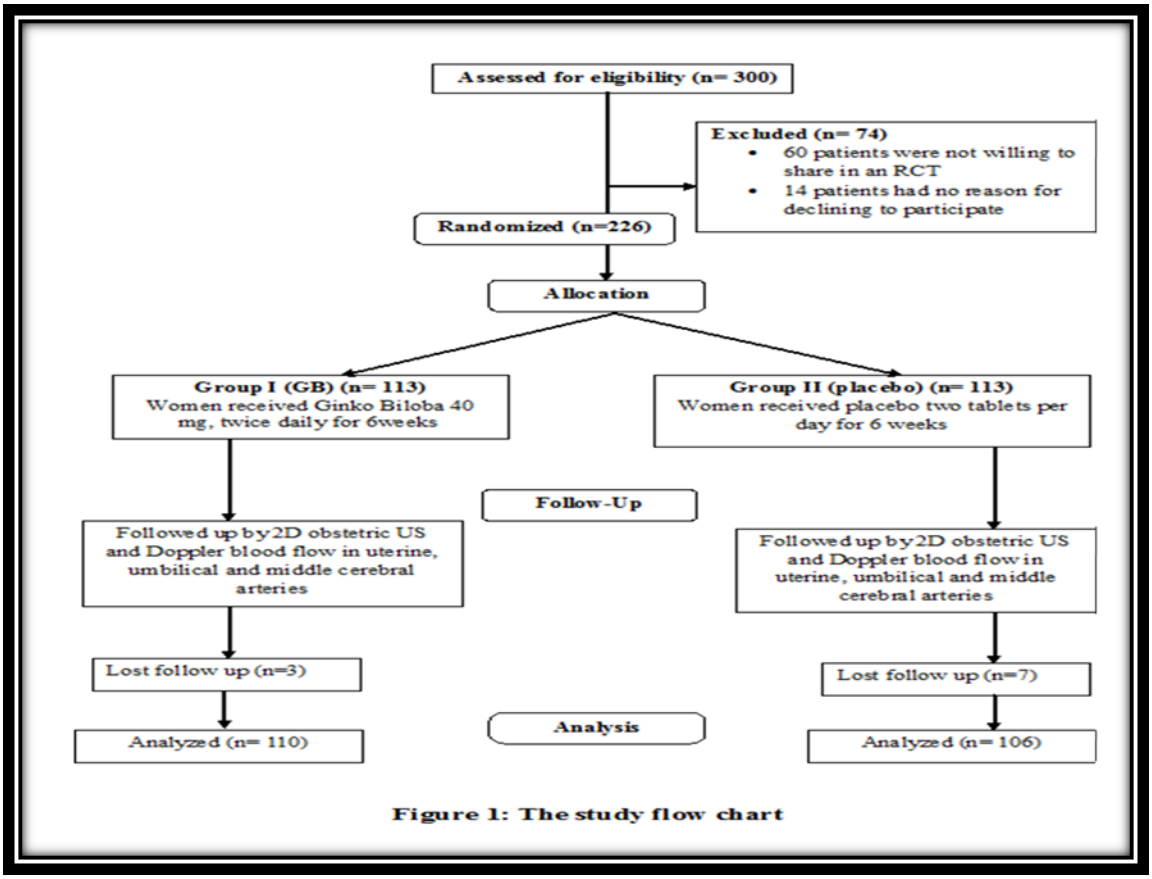

Figure 1: The study flow chart

The demographic characteristics of the participants are shown in Table 1. All studied women were found to be comparable as regard to age, BMI, parity, number of abortions, number of living children, number of previous CS and gestational age at time of recruitment.

As shown in Table 2, both groups were comparable in estimated feral weight at baseline (p=0.81); however, after 6 weeks of treatment, there was a significant increase in the estimated fetal weight (gm) in the GB group when compared to the placebo group (p=<0.001) (Table 2).

As regard Doppler indices (S/D, RI and PI) of the uterine, umbilical and middle cerebral arteries; there were significant increases in blood flow (decreases in Doppler indices) of mentioned vessels in GB group when compared with placebo group (Table 3).

Table 1: Baseline characteristics of the participants

Characteristics	Group I GB (n=113)	Group II Placebo (n= 113)	p value
	Mean ± SD	Mean ± SD	
Age (years)	28.60 ± 6.43	27.50 ± 4.80	0.397
Body mass index (BMI)	23.80 ± 2.23	23.90 ± 1.98	0.874
Parity	2.90 ± 2.20	2.94 ± 1.94	0.870
Number of abortions	0.19 ± 0.52	0.33 ± 0.84	0.515
Number of living children	2.76 ± 1.82	2.93 ± 1.78	0.591
Number of previous CS	0.93 ± 1.51	0.45 ± 0.63	0.482
Gestational age	31.6+ 1.3	31.1+ 1.11	0.426

Table 2: The main study outcomes

Item	Group I GB (n=110)	Group II Placebo (n=106)	p value
	Mean ± SD	Mean ± SD	
	Estimated fetal weight (gm)		
Baseline	1758± 190	1709± 170	0.81
After six weeks	3047± 127	2734± 127	<0.001*

** Statistical significant difference (P < 0.05)*

Discussion

To our knowledge, this is the first randomized clinical study addressing the effect of GB extract on IUGR fetuses. In this study; we found a great benefit of GB extract on feto-placental blood flow. We observed a prominent decrease in Doppler blood flow indices of the uterine, umbilical and middle cerebral arteries after 6 weeks of use which was reflected by significant increase in fetal weight paving the way to put our hand on direct action of GB on maternal and fetal blood vessels.

The rationale behind using this herbal extract in cases of intrauterine growth restriction was its proven ability to act as a free oxygen radical scavenger as well as to improve peripheral vascular circulation. Both actions could hypothetically act in a synergistic fashion to combat IUGR associated hypoxic patho-physiology.[15]

IUGR is one of the most common and complicated problems in modern

obstetrics. The corner stone in the treatment of the asymmetrical IUGR fetus in utero is improvement in utero-placental blood flow.[16] Many approaches have emerged to achieve that goal such as maternal bed rest and maternal hydration which are thought to have a role in increased blood flow to the uterus. The baby aspirin therapy remains controversial but theoretically it serves to preserve or improve blood flow to the placenta.[17] The fish oil which contains omega 3 may be beneficial and many studies proved its great effect on treatment and prevention of IUGR.[18]

Table 3: Doppler blood flow changes in uterine, umbilical and middle cerebral arteries from before to 6 weeks after treatment

	S/D Mean ± SD		p-value	RI Mean ± SD		p-value	PI Mean ± SD		p-value
	Group I GB (n=110)	Group II Placebo (n=106)		Group I GB (n=110)	Group II Placebo (n=106)		Group I GB (n=110)	Group II Placebo (n=106)	
Uterine artery									
Baseline	2.37±1.04	2.33±1.08	0.314	0.51±0.14	0.53±0.15	0.261	0.82±0.38	0.85±0.36	**0.110**
After six weeks	1.65±0.13	2.11±0.33	<0.01*	0.38±0.05	0.46±0.08	<0.01 *	0.56±0.06	0.70±0.08	**<0.01***
Umbilical artery									
Baseline	2.75±0.78	2.76±0.76	0.571	0.61±0.11	0.64±0.12	0.325	0.99±0.28	1.02±0.25	**0.084**
After six weeks	2.04±0.48	2.51±0.54	<0.001*	0.41±0.08	0.52±0.09	<0.001 *	0.56±0.06	0.76±0.08	**<0.001 ***
Middle cerebral artery									
Baseline	5.59±0.94	5.62±0.96	0.541	0.82±0.04	0.85±0.07	0.238	1.79±0.38	1.82±0.39	**0.260**
After six weeks	4.16±0.30	5.10±0.43	<0.001*	0.50±0.02	0.69±0.07	<0.001*	1.12±0.41	1.64±0.44	<0.001*

S/D systolic / diastolic, RI resistant index, PI pulsatility index
** Statistical significant difference (P < 0.05)*

Zadroźna et al. studied placentas from IUGR pregnancies and found statistically significant lower cytochrome-c-oxidase activity of the trophoblast of IUGR and preterm placentas, which positively correlated with both newborn's birth weight and placental weight. Consequently; they proposed hypoxia as one of possible factors leading to a premature birth and IUGR.[19]

The effect of gingko biloba on circulation was proved in several studies. GB can increase cerebral and peripheral blood circulation, reduce vascular permeability, improve venous tone,

inhibit phosphodiesterase type 4 (PDE4), relax vascular smooth muscle via a nitric oxide pathway, and improve blood flow to the corpus cavernosum of the penis.[20]

Other beneficial effects of GB include decreases of systolic and diastolic blood pressure, increases in fasting plasma insulin and C-peptide, decreases of cortisol secretion and decreases in the secretion of corticotropic releasing hormone.[21]

Although women during the child bearing period may use GB for a variety of indications, there are few reports in literature addressing use of GB during pregnancy. This may be because of previous disappointing results reported with the use of GB during pregnancy.

Petty and his colleges in 2001 found a trace of colchicine in the placental blood of pregnant women having taken GB and concluded that GB supplement should be avoided by women who are pregnant or are trying to conceive.[22] However; the GB which was used in their study was adulterated with colchicines because it well known that GB hasn't any colchicines.

Kudolo and his colleges proved that GB has platelet aggregation inhibition effect on animal models.[23] However; they used 120 mg of GB for 3 months (a much higher dose and longer time than we used). So we think that this effect is dose and duration dependent. In addition; no study, up to our knowledge, was conducted on pregnant women and proved that GB may prolong bleeding during delivery.

There is only one systematic review in literature conducted by Dugoua and his colleges in 2006 that addressed the safety and efficacy of GB during pregnancy and lactation. They concluded that GB should be used with caution during pregnancy, particularly around labor where its anti-platelet properties could prolong bleeding time.[8] Moreover; they based their conclusion on animal models and they did not mention any study conducted on humans that proved this conclusion.

We showed significant improvement in Doppler indices values among GB users. We propose that the positive effect of the extract on the placental circulation may be due to the antioxidant effect of GB. Similarly, GB extract significantly increased end diastolic velocity in the ophthalmic artery of glaucoma patients.[24]

We think that our study has many positive points to be mentioned. Firstly; this is the first registered randomized trial that studied the effect of GB on IUGR fetuses. Secondly; it was a double blinded study in which the investigators were blinded regarding the intervention type during the follow up visits. Thirdly; our observations are also consistent with the hypothesis that GB may have a vasodilator effect which opens the way to use it in some important obstetric diseases such as pre-eclampsia and renal diseases which have not been studied before.

Our study had several potential limitations. We used GB extract for only 6 weeks not more, however; the long effect of GB should be emphasized. Despite that we found a significant increase in fetal weight, this may need to be compared to birth weight which is more accurate. Finally; the anti-platelet effect of GB could not be criticized here

because we used GB for 6 weeks only and we haven't information about delivery events; this may be addressed in another study.

Conclusion

The GB extract could improve placental functions, Doppler indices and fetal weight in IUGR fetuses. This effect is mostly due to an oxygen free radical scavenger action combined with a peripheral vascular improvement effect of the herb.

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