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NUTRITIONAL INTERVENTIONS IN REDUCING THE INCIDENCE OF INTRAUTERINE GROWTH RESTRICTION: A REVIEW

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ABSTRACT

Introduction: Intrauterine growth restriction (IUGR) is defined as the failure of embryo to achieve optimal growth of normal range with respect to gestational age and it is one of the major health problems especially in developing countries. The growth of embryo may be affected by several factors, including mother's diet during pregnancy therefore nutritional interventions can be effective in reducing IUGR. This study aims to investigate existing studies and interventions favoring the reduction the Incidence of IUGR.
Method: Google Scholar, Pub med, and Science Direct were used to browse articles in English from 1980 to present with the terms "Intrauterine Growth Retardation" and its abbreviation "IUGR" in combination with "Nutritional" and "Dietary". Academic Jihad database at www.sid.ir and Magiran database at www.magiran.com are also searched for Persian articles.
Result: one Persian article and 14 English studies were selected among 65 articles.
Conclusion: In order to prevent IUGR, it should be most focused on protein / energy consumption while examining the mother's diet in terms of these two nutritional criteria. Also intake of three micronutrients of folic acid, magnesium and vitamin B12 during pregnancy may influence fetal growth.

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Introduction

It is now clear that low birth weight is one of the most important causes of infant mortality while intrauterine growth restriction is one of the most important reasons for LBW (1). According to the American College of Obstetricians and Gynecologists (2001), intrauterine growth restriction (IUGR) is defined as the failure of embryo to achieve optimal growth and body mass of normal range with respect to gestational age (2), and it is one of the major health problems especially in developing countries

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(3). This problem has multiple causes that might result from pregnancy-related hypertension, maternal drug consumption, infection, malnutrition, and other unknown causes (4). Infants infected with this disorder are at increased risk of perinatal mortality, birth hypoxemia, nerve dysfunction, metabolic problems, and metabolic diseases such as type2 diabetes and coronary artery disease in adulthood (5-9). Nutritional support is one of the interventions with significant implications for reducing IUGR as one of the best supplementary interventions (10). The growth of embryo may be affected by several factors, including mother's diet during pregnancy. Several studies have been conducted on animal specimens resulting in the reduction of IUGR through introduction of changes in mother's diet. For example, in a study on animal sample (rat), it was found that the restriction of protein intake in mother's diet led to a reduced fetal growth along with increased blood pressure and intolerance of carbohydrates (13-11). In human population, an epidemiological study was carried out in Netherlands after the Second World War. At this time, people were severely afflicted with food poverty as a result of which the embryos became infected with IUGR and were later found to suffer from intolerance of carbohydrates and metabolic problems in adulthood (10). How nutritional interventions can be effective in reducing IUGR requires further studies as well as a review on the current literature. Therefore, this study aims to investigate existing studies and interventions favoring the reduction of IUGR.

Materials and Methods:

This study is a library review which, according to its nature, investigates related Persian and English electronic literature. Our Persian electronic resources included the Academic Jihad database at www.sid.ir and Magiran database at www.magiran.com. The search strategy was using an unlimited time frame along with the terms: "intrauterine growth restriction" and "intrauterine growth retardation". Google Scholar, Pub med, and Science Direct were used to browse articles in English electronic resources. The term "Intrauterine Growth Retardation" and its abbreviation "IUGR" were searched in combination with the terms "Nutritional" and "Dietary". The time period was considered from 1980 to present. Five papers on intrauterine growth restriction were found in Persian databases among which one was a survey of nutritional interventions. There were 60 articles in English databases among which 15 were consistent with the title of our study and, accordingly, included.

Results:

In Persian databases, five articles were found in one of which regular consumption of calcium and iron supplements were investigated along with other variables. The results showed that regular use of these two micronutrients during pregnancy did not have a significant relationship with IUGR (14). Four other articles did not address food interventions while examining demographic variables.

60 articles were found in English databases 14 papers of which were selected. Our selection criterion of articles was the study of embryo development as a consequence. 10 papers were meta-analyzes extracted from meta-analysis studies of Cochrane baseline most of which were reported in 2002. The results obtained from these studies are presented in Table1.

Table1: Studies investigating the impact of nutritional interventions on Incidence of Intrauterine Growth Restriction

No.	author	Publication year	title	sample	intervention	result	Reference no.
1	VIEGAS & et al.	1982	Dietary protein energy supplementation of pregnant Asian mothers at Sorrento, Birmingham. II: Selective during third trimester only	Forty-five mothers who at 28 weeks were known to be nutritionally at risk and Eighty-three mothers regarded as adequately nourished at 28 weeks	Three groups: (a) vitamins only-a multivitamin sachet daily containing vitamins A, B, C, and D; (b) energy- 42-125 MJ (10 000-30 000 kcal), all from carbohydrate plus vitamins; (c) protein energy and vitamins as before, but with 5-10% of	Supplementation did not lead to improved intrauterine growth in those mothers who were adequately nourished.	15

					energy from milk protein.		
2	Bulstra-Ramakers & et al	1995	The effects of 3g eicosapentaenoic acid daily on recurrence of intrauterine growth retardation and pregnancy induced hypertension	Sixty-three women with a history of intrauterine growth retardation (birth weight < 10th centile) with or without pregnancy induced hypertension in the previous pregnancy.	3 gr Eicosapentaenoic acid or placebo were given from 12 to 14 weeks of gestation onwards.	There were no differences between eicosapentaenoic acid and placebo group	16
3	ONWUDE & et al	1996	A RANDOMIZED DOUBLE BLIND PLACEBO CONTROLLED TRIAL OF FISH OIL IN HIGH RISK PREGNANCY	Two hundred and thirty-three pregnant women at high risk of developing proteinuric or nonproteinuric pregnancy induced hypertension or asymmetrical intrauterine growth retardation	Two group: placebo vs. 2.7 g of MaxEpa daily (1.62 g of eicosapentaenoic acid and 1.08 g of docosahexaenoic acid)	There is no evidence from this study for any useful effect of fish oil supplementation for women at high risk of adverse outcomes from a pregnancy	17
4	Olsen & et al	2000	Randomized clinical trials of fish oil supplementation in high risk pregnancies	Four prophylactic trials enrolled 232, 280, and 386 women who had experienced previous pre-term delivery, intrauterine growth retardation, or pregnancy induced hypertension respectively, and 579 with twin pregnancies. Two therapeutic trials enrolled 79 women with threatening	fish oil provided 2.7 g and 6.1 g n-3 fatty acids/day in the prophylactic and therapeutic trials	Fish oil had no effect on intrauterine growth retardation	18

				pre-eclampsia and 63 with suspected intrauterine growth retardation			
5	Kramer, M	2002	Balanced protein/energy supplementation in pregnancy (Cochrane Review)	Thirteen trials, involving 4665 women,	Energy/protein supplementation for pregnant women in which the protein content of the supplement was 'balanced' (protein content less than 25% of total energy content).	Balanced energy/protein supplementation improves fetal growth and may reduce the risk of fetal and neonatal death	19
6	Kramer, M	2002	Isocaloric balanced protein supplementation in pregnancy (Cochrane Review)	Three trials involving 966 women	All acceptably controlled comparisons of isocaloric protein supplementation , as long as the protein content of the supplement was 'balanced', ie the protein provided <25% of its total energy content	Balanced protein supplementation alone (ie without energy supplementation) is unlikely to be of benefit to pregnant women or their infants	20
7	Duley, L. & Henderson-Smart, D	2002	Reduced salt intake compared to normal dietary salt, or high intake, in pregnancy (Cochrane Review)	Two trials were included, with 603 women	a low salt diet with no dietary advice	No significant effect on SGA reduction	21
8	Mahomed, K	2002	Iron supplementation in pregnancy (Cochrane Review)	Twenty trials were included	Iron supplementation	No significant effect on fetal growth	22
9	Cuervo, L. G. & Mahomed, K	2002	Treatments for iron deficiency anemia in pregnancy (Cochrane Review)	Five trials, involving approximatel y 1234 anemic women	IRON supplementation	No significant effect on fetal growth and LBW reduction	23
10	Makrides, M. & Crowther, C. A	2002	Magnesium supplementation in pregnancy (Cochrane Review	Ten trials involving 9090 women	magnesium was administered orally at any time during the antenatal period, regardless of dose	no statistically significant effects of magnesium supplementation on	24

						the frequency of perinatal mortality or small-for-gestational age infants when compared with placebo or no treatment	
11	Mahomed, K	2002	Zinc supplementation in pregnancy (Cochrane Review). In: The Cochrane Library,	included 21 randomized controlled trials (RCTs) reported in 54 papers involving over 17,000 women and their babies	zinc supplementation in pregnancy	No significant effect on fetal growth and SGA	25
12	Mahomed, K. & Gulmezoglu, A. M	2002	Vitamin D supplementation in pregnancy (Cochrane Review).	Two trials involving 232 women	vitamin D supplementation during pregnancy	In one trial the mothers had higher mean daily weight gain and lower number of low birth weight infants. In the other trial the supplemented group had lower birth weights	26
13	Hofmeyr, G. J., Atallah, A. N. & Duley, L	2006	Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems	12 trials, 15,206 women	comparing at least one gram daily of calcium during pregnancy with placebo	There was no overall effect on the relative risk of the baby being born small-for-gestational age	27
14	Muthayya & et al	2006	Low maternal vitamin B12 status is associated with intrauterine growth retardation in urban South Indians	478 women were recruited at 12.973.3 weeks of gestation	Prospective observational study	vitamin B12 deficiency in pregnancy combined with appropriate interventions are likely to play an important role in reducing IUGR	28
15	SH Jahanian Sadatmahale & et al	2011	Effect of Some Risk Factors Associated with Intrauterine Growth Retardation (IUGR)	Fifty hundred four pregnant women, between the age of 18 and 35 years	cross-sectional, descriptive-analytical study(in Persian)	IUGR is higher in woman whose weight gain was lower than normal rang, female newborn and housekeeper mothers. There	14

						is a direct link between IUGR and the history of chronic disease in mothers.	

According to the previous studies, limitation of protein and energy intake during pregnancy leads to IUGR in animals of laboratory (29). These conditions apply to humans conveying that the restrictions of energy and protein intake might cause IUGR (19, 30). In a systematic review, it was found that supporting mothers in order for them to receive enough energy / protein would make IUGR less likely to occur. The odds ratio reported by these researchers was 0.77 ($P < 0.05$). In another study in Chile, it was found that the pregnant mothers who had received the kind of milk enriched with vitamins and minerals had experienced less IUGR compared to the control (32% vs. 44% $P<0.05$) (31). Another study was conducted in Tanzania reporting the mothers who received multivitamin capsule (containing riboflavin, niacin, thiamine, vitamins B6, B12, C, E, and folic acid) were at lower risk of IUGR compared to the group who received placebo (10% vs. 18% $P = 0.002$) (31). In general, nutritional interventions for IUGR reduction could be categorized into two: micronutrients (including vitamins and minerals) and protein-energy intake, which are discussed below.

Interventions in the daily diet:

Protein-energy balance: In a systematic review on 13 clinical trials, it was found that the balance in protein-energy intake could reduce the intrauterine growth restriction with an average of about 32% (19). On the other hand, another meta-analysis study found that supplementation with high protein content would reduce fetal weight with respect to the gestational age (SGA); also, it is harmful to the fetus. In this meta-analysis, a clinical trial study, among three studies, was conducted investigating the effects of high-protein diet on the SGA (20). One clinical trial study revealed that supporting pregnant mothers with a balanced diet of energy-protein during their third trimester of pregnancy did not have a significant effect on IUGR reduction (26).

Reducing salt intake: In a systematic review on two clinical trials, it was found that salt reduction does not have significant effects on IUGR or SGA. In these trials, the effect of a diet including recommended amount of salt versus a diet of high amounts of salt was investigated on fetal growth (21).

Micronutrient supplements:

Calcium supplement: Calcium is prescribed to control blood pressure during pregnancy which also leads to the development of embryo. For example, a study in India investigated calcium's effect on fetal growth reporting that it did not have any significant effect. However, the sample size of this study was small. Also, another study in United States did not report any significant effect of calcium supplement on the incidence of IUGR and SGA (32). In a meta-analysis, 11 articles were examined which measured the effect of calcium during pregnancy and its outcomes. Mixed results of decreasing SGA were reported in nine articles investigating its effects on fetal growth. Still there was a significant decrease of 17% in the incidence of LBW which was due to an increase in the length of pregnancy and its effect on fetal growth (27).

Iron supplement: In a systematic review of 20 experimental studies, it was found that supplementation with iron did not have any significant changes in fetal development (22). Another study reported that supplementation of pregnant mothers during pregnancy only led to a slight increase in birth weight which was not statistically significant (31).

Folic Acid: Studies on these micronutrients have reported mixed results. Major studies have suggested the effect of these micronutrients on reducing the risk of LBW (33). Some studies have also examined the simultaneous effects of folic acid and iron supplements on fetal growth the results of which support the effect of these two on birth weight. Although, due to the small sample size of these studies, the results were not reliable (31). A study by Liu et al. (2014) found that IUGR had an effect on lipid metabolism and, also, the use of folic acid during pregnancy prevented the modification by regulating DNA methylation in the promoter (34).

Magnesium: the effect of this micronutrient on pregnancy outcomes has been investigated in several studies. In seven clinical trials, magnesium supplementation has been shown to influence SGA. Combining the results of these studies in a review, a 30% reduction in SGA risk was observed (24). In another study, the results of four clinical trials were reviewed and analyzed. It was found that pregnant mothers who were supplemented with magnesium during pregnancy had a birth weight of 51 grams more than the mothers who did not receive these micronutrients (31).

Zinc: The results of a systematic review have shown that Zinc supplementation does not have significant effects on the reduction of SGA risk (25). Other studies have also shown that the use of zinc during pregnancy also has no significant effect on birth weight (31).

Vitamin D: Studies on this supplement are limited and the results of these studies have not provided evidence supporting the significant effect of this supplement on the reduction of SGA risk (26).

Vitamin C and E: examining the one study on this supplement also indicates that the use of these two micronutrients does not have a significant effect on reducing the risk of SGA (31).

Vitamin B12: In a study by Muthayya et al. (2006), it was reported that vitamin B12 deficiency was associated with IUGR, and suggested that during pregnancy, the mother's condition should be checked, taking the necessary action in case of deficiency (28).

Fish oil: a meta-analysis that used the data from four studies indicated that fish oil consumption during pregnancy had no significant effect on fetal growth (18). The results of another clinical study also suggested that fish oil did not influence fetal growth and having no supportive effect on IUGR (17).

Conclusion:

Intrauterine growth retardation is an important risk factor for LBW and neonatal death. Observations and studies conducted in different parts of the world have shown that the socioeconomic conditions, the level of mother's literacy and dietary nutrition can affect the restriction of intrauterine growth. A review of various studies on animal and human samples shows that receiving recommended amounts of protein and energy during pregnancy is an appropriate nutritional intervention to reduce the incidence of IUGR. And the intake of three micronutrients of folic acid, magnesium and vitamin B12 during pregnancy also has anticipatory effects on the disorder. Several studies have also been carried out on the use of micronutrients that have been shown to significantly reduce the incidence of IUGR. However, considering the number of studies conducted and the validity their provided evidence, it is clear that in order to prevent IUGR, it should be most focused on protein / energy consumption while examining the mother's diet in terms of these two nutritional criteria.

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