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INTRAUTERINE GROWTH RESTRICTION (IUGR) AS PART OF FETAL ALCOHOL SYNDROME: A REVIEW ARTICLE

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ABSTRACT

INTRODUCTION: An investigation was conducted on the effects of alcohol on pregnant women as a possible cause of intrauterine growth restriction. The American Pregnancy Association defines intrauterine growth restriction (IUGR) as a fetal weight below the 10th percentile for gestational age as determined by ultrasound. **METHODOLOGY:** A search of medical literature was performed from January 2010 to January 2022. For this purpose, different scientific databases were used, which were: PUBMED, EBSCO and Google Scholar. **RESULTS:** The fetal period is the time of development from the ninth week to the moment of birth. The most severe form associated with alcohol consumption during pregnancy is Fetal Alcohol Syndrome, which requires a minimum consumption of 12 g per day of absolute alcohol for this syndrome to manifest itself. Infants whose mothers are chronic alcoholics show a characteristic pattern of defects including prenatal and postnatal growth deficiencies, mental deficiency, and other problems. **DISCUSSION:** Environmental factors influence fetal growth, and this has been increasingly emphasized with increasing evidence. Regarding the database collected from different research sources, it's confirmed that great relationship that exists on the effects of alcohol consumption by pregnant women on fetal growth. Kazutoshi-cho's study on prenatal exposure to alcohol in Japanese women shows that the consumption of a weekly dose of alcohol during the second and third trimester has a significant negative effect with the decrease in body weight, body length and head circumference at birth. **CONCLUSION:** Excessive alcohol consumption is highly associated with fetal growth restriction (fetal alcohol syndrome). The level of effects may be different depending on the frequency of exposure and dose.

KEYWORDS: *fetal growth retardation; pregnancy; alcoholism, "toxic substances", "fetal development".*

INTRODUCTION

A normal fetal growth is a fundamental and critical element of healthy mating and influences the long-term health of the offspring. However, determining normal and abnormal fetal development has been a challenge in clinical practice and research. Prenatal alcohol exposure is one of the causes of somatic, cognitive and behavioral changes that, along with the end of fetal alcohol spectrum disorder (FASD)[1], these disorders are known to result from prenatal alcohol exposure and include fetal alcohol syndrome (FAS).

Fetal alcohol syndrome is a pattern of physical, behavioural, and mental disorders that occur in newborns whose mothers consumed alcohol during pregnancy. These abnormalities

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occur primarily at the onset of embarrassment, when the fetus is most susceptible to the teratogenic effects of alcohol[2].

Maternal and fetal alcoholism is not widely recognized and is extremely important in the development of many neuropsychiatric disorders in children, adolescents and adults (disorientation, confusion, insomnia, hallucinations, depression, Korsakoff syndrome, etc.). Currently, there are several functional and structural effects associated with ethanol consumption by shamed women, especially in terms of fetal central nervous system (CNS) development[3].

During research on birth defects due to fetal alcohol syndrome, several specific forms of malformations, developmental delay and CNS dysfunction were identified in some children of alcoholic mothers[4].

Its early diagnosis is of great importance for primary prevention through total abstinence during embarrassment and secondary prevention in neonates and children for adequate follow-up that reduces the risk of side effects.

The fetal alcohol syndrome can be evidenced in those patients who have intrauterine growth restriction, this is defined as the pathological inhibition of intrauterine fetal growth and the inability of the fetus to reach its growth potential[5].

IUGR has multiple multifactorial causes and, in addition to, complex management for the obstetrician. For the fetus, the fact that it does not reach its development potential greatly increases perinatal morbidity and mortality. Inadequate fetal nutrition is one of the main causes of IUGR, regardless of whether its origin is maternal or placental[6].

Normal fetal growth is regulated by several factors such as maternal, fetal and placental. The normal functioning of these three factors allows the fetus to grow to a genetically predetermined height and weight[1]. In addition to perinatal morbidity, there is evidence linking intrauterine growth restriction to significant metabolic and cardiovascular changes in adulthood[1].

Another important term within intrauterine growth restriction is Small Gestational Age (SGA), which refers to the fetus with fetal growth below expectations, defined by an estimated fetal weight below the 10th percentile for its gestational age[7].

METHODOLOGY

A descriptive observational study was carried out in which a search was carried out in the medical literature from January 2010 to January 2022. For this, different scientific databases were used, which were: PubMed, EBSCO and Google Scholar.

Before starting the search, the boolean descriptors: "fetal growth retardation", "pregnancy", "alcoholism", "toxic substances", "fetal development", were obtained from Life Sciences Descriptors. Including only literature in English and Spanish.

Inclusion criteria:

- Articles indexed in health sciences databases.
- In English and Spanish.
- Published in 2010 to 2022.

Exclusion criteria:

- Studies published before 2010 were excluded.

RESULTS

Fetal period

This is the developmental time from the ninth week to the time of birth. It is related to the rapid growth of the body and the differentiation of tissues, organs and systems.

From a clinical point of view, the gestational period is divided into three trimesters. By the end of the first quarter, all major systems had been developed. During the second trimester, the fetus acquires a sufficient size, during this period most birth defects can be detected by real-time high-resolution ultrasound. At the beginning of the third trimester of pregnancy, the fetus can survive even if the delivery is premature[8,9].

Highlights of the fetal period (Table 1):

Table 1. Highlights of the Fetal Period

Age (weeks)	Main external features
Week 9	The eyelids close or are closed. The head is large and rounder. It's not possible to differentiate the male and female external genitalia. Some intestinal loops can be in the proximal part of the umbilical cord.
Week 10	The intestinal loops are located in the abdomen. Initial development of fingernails.
Week 12	The external genitalia make it possible to differentiate between the male and female sexes. The neck is well defined.

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Week 14	The head is held erect. The eyes look forward. The lower limbs are well developed. Initial development of toenails.
Week 16	The ears protrude from the head.
Week 18	Caseous vernix covers the skin. The mother perceives the first fetal movements.
Week 20	Head and body hair (lanugo) is visible.
Week 22	The skin is smooth, translucent, and pinkish or reddish in color.
Week 24	Fingernails are present.
Week 26	The eyelids are partially open. The tabs are visible.
Week 28	The eyes are fully open. The skin is slightly wrinkled.
Week 30	The nails of the toes are observed. Testicles in descent phase.
Week 32	The fingernails reach the fingertips of the hands. The skin is smooth.
Week 36	The body is generally plump. There is almost no lanugo. Limbs in flexion; firm grip.
Week 38	Prominent chest; breast protrusion. The testicles are in the scrotum or are palpable in the inguinal canals.

Stubtitles: Moore KL, Persaud TVN, Torchia MG. Embriología Clínica. 11ª ed. Barcelona, España: Ed. Elsevier Saunders. 2020.

Weeks 9 to 12: By the beginning of the ninth week, the head constitutes approximately half of the occipital-coccyx length of the fetus, and by the end of the 12th week, the occipital-coccyx length has more than doubled, due to accelerated body growth. At 9 weeks, the liver is the main organ where erythropoiesis occurs. The primary centers of ossification, especially in the skull and large bones, appear towards the end of sweetest. During these weeks of gestation, measurement of nuchal translucency (NT) is essential as an early diagnostic study for chromosomal disorders (figure 1) [8,9].

FIGURE 1. Ultrasound in a fetus of 12 weeks of gestation in which Nuchal translucency is evaluated

Source: Authors.

Weeks 13 to 16. During this period, fetal growth development is rapid. Fetal skeletal ossification remains active and bones are highly visible on ultrasound[8,9].

Weeks 17 to 20. During this period, growth slows down, the occipital-coccyx length increases by approximately 50 mm. The mother is usually aware of fetal movements. Furthermore, the skin is covered by vernix caseosum (a mixture of dead epidermal cells and fatty material from the sebaceous glands) [8,9].

Week 21 to 25. In this period there is an increase in body weight and the fetus acquires a better proportion. Type II pneumocytes begin to secrete surfactant. Premature babies born in this period can survive in intensive care, but they can die due to the immaturity of the respiratory system[8,9].

Weeks 26 to 29. If labor occurs during this time, the fetus usually survives as long as it receives intensive care. The lungs and pulmonary vasculature were sufficiently developed to allow gas exchange to take place. The CNS has matured such that it can direct rhythmic breathing movements and control body temperature[8,9].

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Weeks 30 to 34. The pupillary reflex can be induced at 30 weeks. During this period, white adipose tissue represents approximately 8% of the total body weight. Fetuses born prematurely at 32 weeks or more usually survive[8,9].

Weeks 35 to 38. Fetuses born at 35 weeks have firm attachment and show spontaneous orientation toward the light. As delivery approaches, the growth rate slows down.

At term, most fetuses reach an occipital-coccyx length of 360 mm and a body weight of approximately 3400 g [8,9].

Fetal alcohol syndrome

Alcohol is one of the most common and important substances that affect brain development, and its use during pregnancy can cause a variety of physical, cognitive and behavioural abnormalities. It is one of the leading non-genetic causes of preventable birth defects and varying degrees of intellectual disability.

The most serious form associated with alcohol consumption during pregnancy is Fetal Alcohol Syndrome. For this syndrome to manifest, a minimum consumption of 12 g per day of absolute alcohol is required, equivalent to 100 cc of wine, 300 cc of beer and 25 cc of whiskey[10].

Alcohol exposure in utero is the most common preventable cause of intellectual disability. This syndrome includes malformations and neurodevelopmental disorders. In addition, newborns with fetal alcohol syndrome may have high blood alcohol concentrations at birth, alcoholic breath, hyperactive phase, tremors, irritability, and even seizures[11,12].

The incidence of this condition is 1 in 13 newborns exposed to it, this would translate to 630,000 children born per year in the world[13]. Adverse effects on pregnancy outcomes may also be seen, including increased risk of miscarriage, placental abruption, preterm delivery, intrauterine stillbirth, and sudden fetal death[14].

In the studies and articles analyzed, high data was observed in women who continue to consume alcoholic beverages despite their state[15]. A study found that 40.7% of women had consumed alcohol during the first trimester, decreasing their consumption in the second and third trimesters to 23.1% and 17% respectively due to the interventions by health personnel[16].

This excessive consumption of alcohol in pregnancy usually occurs with a high prevalence in populations with greater economic and social marginalization, as well as in indigenous communities[13]. Consumption of alcohol and other harmful substances in pregnant women can be related to factors such as stress, immaturity, unplanned pregnancy, religion, and mental illnesses such as depression[11,15]. Growth failure is classified as one of the characteristic symptoms, usually recorded when height or weight falls below the 10th percentile of growth charts[17]. It can be classified into different degrees depending on the severity (Table 2).

Table 2. Classification of growth retardation in the newborn according to severity

Grade	Description
Severe	Height and weight equal to or less than the 3rd percentile.
Moderate	Anyone of height or weight at or below the 3rd percentile, but not both.
Mild	Both height and weight between the 3rd and 10th percentiles.
None	Height and weight above the 10th percentile.

Subtitles: Denny, L., Coles, S., & Blitz, R. (2017). Fetal Alcohol Syndrome and Fetal Alcohol Spectrum Disorders. American Family Physician, 96(8), 515–522.

Facial deformities are another important clinical characteristic; short palpebral fissures, palpebral ptosis, flattened and wide nasal bridge, epicanthal fold, hypotelorism, strabismus, maxillary hypoplasia, short nose, thin upper lip, micrognathia, changes in the auricles and microcephaly, many cases are associated with cardiac abnormalities and skeletal deformities[14,17,18].

The alterations of the CNS are due to an inhibition of ganglioside biosynthesis and some effects of phosphorylation of proteins associated with microtubules and neurotropic factors, generally seen as hypoplasia of the corpus callosum and cerebellum, gliosis, reduced volume of the striatum, pituitary hypoplasia, cavum septum pellucidum, and thalamic dysfunction[14,19].

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The diagnosis of this syndrome is clinical, based on the manifestations that occur in the fetus; however, new methods have been established, such as biomarkers of exposure to alcohol in hair and meconium, which have been more effective[17].

It is necessary to abandon alcohol consumption prior to pregnancy or at the beginning of it to prevent the development of this type of complications, which affect the development of the fetus and lead to possible long-term problems in the newborn.

Intrauterine Growth Restriction (IUGR)

IUGR is the inability of the fetus to reach its genetic potential for growth due to the adverse environment during pregnancy, resulting in a secondary decline in fetal growth rate after the first trimester.

For the World Health Organization (WHO), any fetus whose birth weight is less than 2,500 g is defined as "low birth weight" regardless of gestational age[20].

Epidemiologically, 8% of pregnancies develop IUGR, so it is believed to be a worldwide clinical problem, which develops a higher incidence of fetal death.

The main measurable feature of IUGR is low birth weight below the 3rd percentile (normalized for gestational age and sex) or below the 10th percentile (accompanied by signs of fetal compromise), with the option of having evidence of abnormal cord blood flow to the Doppler examination (Table 3)[21]. Likewise, FGR is known to have short-term and long-term consequences such as cardiovascular, kidney, immune and neurological diseases that have a significant impact on humans and society[22].

Table 3. Classification according to Doppler evaluation in fetus with IUGR.

Normal	Estimated fetal weight 3-10th percentile, fetal Doppler and normal uterine arteries	
Type I	Estimated fetal weight percentile < 3 + normal Doppler any Estimated fetal weight percentile < 10 with: Percentile of brain-placenta ratio < 5 Umbilical artery pulsatility index percentile > 95 Middle cerebral artery pulsatility index percentile < 5 Uterine artery pulsatility index percentile > 95	Follow-up weekly
Type II	Estimated fetal weight percentile < 10 with: Absent diastolic flow in the umbilical artery Reverse diastolic flow in the aortic isthmus	Follow-up every 72 hours
Type III	Estimated fetal weight percentile < 10 with: Reverse diastolic flow in the umbilical artery Duct venosus pulsatility index > 95th percentile	Follow-up every 24 to 48 hours
Type IV	Estimated fetal weight percentile < 10 with: reverse diastolic flow in the ductus venosus Spontaneous decelerations in the cardiotocographic record	Follow-up every 12 hours

Subtitles: Raul A. García Posada & José Enrique Sanín Blair. (2016). Manejo y seguimiento del feto pe-queño y del feto con restricción del crecimiento intrauterino. Memorias Curso de Actualización en Ginecología y Obstetricia, 25, 22.

Associated with fetal alcohol syndrome, it is recognized that it is related to the hypoxia to which they are subjected and to the transient decrease in placental blood flow during childbirth, situations that condition craniofacial malformations and neural deficits[6].

Some studies document that these fetuses are characterized by impaired glucose synthesis and have higher risks of developing T2DM in adulthood[23].

Moderate and high levels of alcohol consumption during the early stages of pregnancy can cause changes in the growth and morphogenesis of the embryo and fetus. Infants born to mothers who are chronic alcoholics show a characteristic pattern of defects that includes prenatal and postnatal growth deficiencies, mental deficiency, and other problems (Figures 2 and 3).

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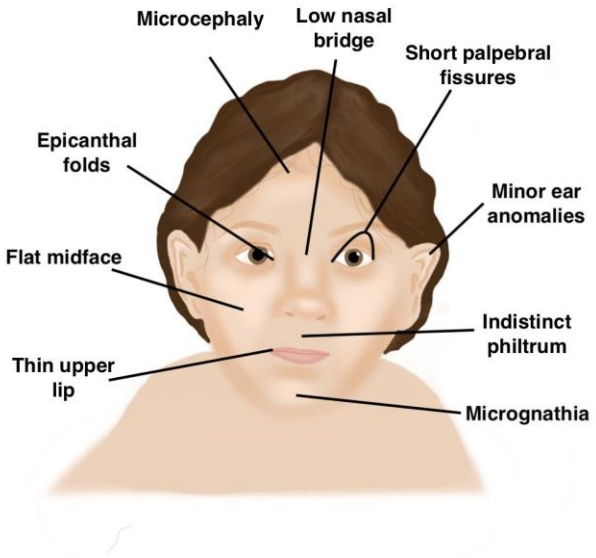
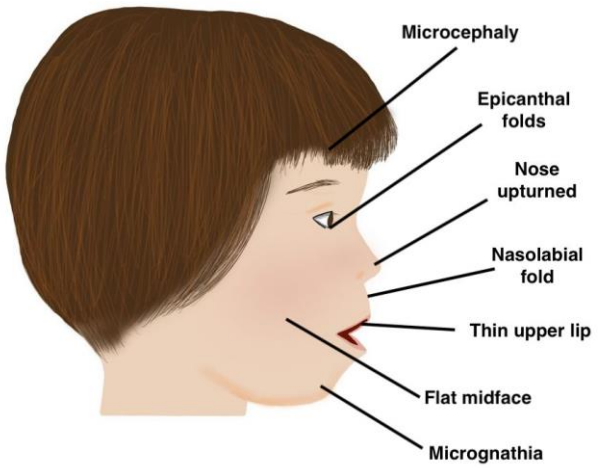
FIGURE 2. Front view: Dysmorphic features of fetal alcohol syndrome in na infant.



Source: Authors.

FIGURE 3. Side view: Dysmorphic features of fetal alcohol syndrome in na infant.



Source: Authors.

DISCUSSION

Environmental factors influence fetal growth, and this has been increasingly emphasized with increasing evidence. This period of growth is important because of the rapid rate of cell proliferation and organ differentiation, which is sensitive to the smallest environmental changes. One of the most important stressors is alcohol consumption, which is highly associated with intrauterine growth restriction due to fetal alcohol syndrome. Alcohol easily crosses the placenta, so may indirectly alter fetal advancement by disrupting normal hormonal interactions between mother and fetus.

Regarding the database collected from different research sources, it's confirmed that great relationship that exists on the effects of alcohol consumption by pregnant women on fetal growth. Kazutoshi-cho's study[24] on prenatal alcohol exposure in Japanese women shows us that the consumption of a weekly dose of alcohol during the second and third trimester has a significant negative relationship with the decrease in body weight, body length and head circumference at birth, data consistent with the results fetal development times presented in Table 1. In this same study we can also note that the level of effects of alcohol consumption during pregnancy can vary depending on the frequency of exposure to alcohol, duration, dose, maternal nutrition, genetic factors and the stage of development in which the fetus is exposed, the figures he gets according to the results obtained are that the consumption of more than 5,20 and 100 grams per week during the second and third trimesters can affect fetal growth, similarly, an article in the Chilean Journal of Pediatrics mentions that the average intake of one drink per day (12 grams of alcohol) puts the fetus at risk for growth retardation and other alcohol-related defects[10].

However, this information remains controversial, as there are studies that report that even if these women had consumed lower levels of alcohol during pregnancy, they could affect fetal growth, while case-control studies mention that light or moderate alcohol consumption does not affect intrauterine growth[25]. These discrepancies may be due to differences in study methodology or misclassification regarding alcohol exposure, as well as differences in universal values. New studies are needed that focus on the effects of alcohol at low and moderate levels in the fetal phase, in order to confirm that even the lowest consumption of alcohol can affect the fetus.

Alcohol consumption among young women turns out to be a habit that usually remains even after conception. In a birth cohort study by the Japan Children's and Environmental Survey, the rate of alcohol use among pregnant women before and after pregnancy awareness was 50% and 2.8%, respectively[26].

The data obtained are of great relevance and importance to intervene in the awareness and promotion of a healthy lifestyle in prenatal care through education and government interventions on the harmful effects of alcohol in pregnancy, not only due to the association between fetal alcohol syndrome and intrauterine growth restriction, if not learning disabilities, miscarriages, structural malformations, CNS damage, and neurodevelopmental abnormalities.

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CONCLUSION

IUGR is the inability of the fetus to reach its genetic potential for growth due to the adverse environment during pregnancy, resulting in a secondary decline in fetal growth rate after the first trimester. Excessive alcohol consumption is highly related to fetal growth restriction (fetal alcohol syndrome). The level of the effects may be different depending on the frequency of exposure and dose.

CONFLICT OF INTEREST

The authors state that there are no conflicts of interest.

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