The effects of alcohol consumption on fetal craniofacial development during gestation: a systematic review

Os efeitos do consumo de álcool no desenvolvimento craniofacial fetal durante a gestação: uma revisão sistemática

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ABSTRACT
The present study used evidence-based dentistry (EBD) to identify clinical studies that described the effects of alcohol on fetal craniofacial development and qualitatively analyze the results found via this systematic review. This systematic review followed the guidelines “Meta-analysis Of Observational Studies in Epidemiology” (MOOSE). As a research strategy, several medical and scientific platforms were chosen, in which studies were sought using keywords defined from medical subject headings (MeSH), following

the criterion of choosing keywords that were most related to the proposed theme. A total of 278 studies (116 studies in humans and 162 studies in animals) were identified and, after screening and analysis based on the inclusion criteria, twenty-six observational studies in humans were chosen for the configuration of this systematic review. Studies have reported fetal alterations related to alcohol consumption by mothers such as in the head shape and size, thin upper lip, hypoplastic philtrumbone, short palpebral fissures, micrognathia, flat nasal bridge, among others. These were more often found in patients whose mothers were alcoholics or those who had ingested high doses of alcohol, especially during the first trimester of gestation. Based on the analysis of the results, the impact of maternal alcohol consumption on fetal craniofacial development was evidenced and, as such, these complications can be harmful to the quality of life of the patient, both in childhood and in adulthood, as well as leading to lifelong sequelae. The results also suggest that to avoid craniofacial anatomical abnormalities related to alcohol, the best course of action is to stop alcohol consumption completely or at least reduce it to a minimum level before conception.

Keywords: alcohol, embryo, facial anomaly, fetus, gestation.

RESUMO

O presente trabalho por meio da Odontologia Baseada em Evidência (OBE), teve como objetivo identificar estudos clínicos que descreveram os efeitos do álcool no desenvolvimento craniofacial fetal e analisar qualitativamente os resultados encontrados nesta revisão sistemática. A presente revisão sistemática foi desenvolvida seguindo as diretrizes em "Meta-análise de estudos observacionais em epidemiologia" (MOOSE). Para estratégia de pesquisa, diversas plataformas médicas e científicas foram eleitas, nas quais foram buscados estudos usando palavras-chaves definidas a partir do MeSh, seguindo o critério da escolha de palavras-chave que mais tinham relação com o tema proposto. Um total de 278 artigos (116 estudos com humanos e 162 estudos com animais) foram identificados e, após triagem e análise baseada nos critérios de inclusão, vinte e seis estudos observacionais em humanos foram eleitos para a configuração desta revisão sistemática. Os estudos relataram alterações fetais relacionadas ao consumo de álcool pelas mães como no formato e tamanho da cabeça, lábio superior fino, filtro hipoplásico, fissuras palpebrais curtas, micrognatia mandibular, ponte nasal plana e outras alterações, sendo mais frequentemente encontradas em pacientes cujas mães eram alcoólatras ou que ingeriram doses elevadas de álcool principalmente durante o primeiro trimestre de gestação. Com base na análise dos resultados, evidenciou-se o impacto do consumo materno de álcool sobre o desenvolvimento craniofacial fetal e que estas complicações podem ser danosas para a qualidade de vida do paciente, tanto na infância, quanto na vida adulta, podendo levar sequelas por toda vida. Os resultados também sugerem que para evitar completamente as anormalidades anatômicas craniofaciais relacionadas ao álcool, o conselho para interromper o consumo de álcool ou pelo menos reduzi-lo a um nível mínimo antes da concepção é clinicamente recomendado.

Palavras-chave: álcool, anomalia facial, embrião, feto, gestação.

1 INTRODUCTION

Alcohol and drug use among pregnant women has experienced a significant increase in recent decades (Sebastiani *et al.*, 2018, Lee *et al.*, 2020). The gestational

period represents a delicate phase of the reproductive process and is subject to various physiological changes that are influenced by the mother's diet, habits in relation to physical activity, smoking and alcoholic beverages (Caro, 2020).

With regard to alcohol intake, it can be said that the embryo is more sensitive to alcohol at the beginning of its development, in the gastrulation phase, which occurs in the third week of gestation (Eberhart *et al.*, 2017). Gastrulation is one of the key events in the development process by which the embryo of pluripotent cells diversifies into specific cell lines (ectoderm, mesoderm and endoderm), which will result in the formation of the adult individual. This stage is also the beginning of morphogenesis, a process that begins with the formation of the primitive line that results from the proliferation and migration of cells from the epiblast to the median plane of the embryonic disc. It is still at this stage that the progenitor cells of the central nervous system and the formation of the facial features of the embryo begins, making this moment even more relevant (Pijuan-Sala *et al.*, 2019, Tyser *et al.*, 2020).

It is in the gastrulation stage that the alcohol ingested by the mother can easily cross the placental barrier and make contact with the embryo, affecting cell migration and consequently morphogenesis (Price *et al.*, 2017). In addition, each additional week of exposure to alcohol during the first trimester significantly increases the risk of miscarriage, even at low levels of consumption (Sundermann *et al.*, 2021).

Exposure to alcohol is one of the risk factors for the birth of children with low weight, microcephaly, craniofacial anomalies, skeletal and/or organ defects (Price *et al.*, 2017, Zhang *et al.*, 2021). It also increases the risk of congenital problems, including fetal alcohol spectrum disorder (FASD) and its most severe form, fetal alcohol syndrome (FAS) (Oei, 2020). Although the consumption of alcoholic beverages by pregnant women is not considered to be high, studies suggest that even moderate alcohol intake can be harmful to fetal development and can cause growth retardation (Lee *et al.*, 2020).

To obtain more information on the effects of alcohol and specifically on the craniofacial development of the embryo, the use of a systematic review allowed us access to a vast amount of research, and it was possible to correlate them through evidence-based dentistry (EBD). As a contribution, EBD has introduced methods that generate quality evidence, statistical tools used to synthesize and analyze evidence (systematic reviews and meta-analysis), and ways to access (electronic databases) and apply evidence (evidence-based health decisions) (Zina *et al.*, 2012).

2 MATERIAL AND METHODS

This systematic review was submitted to the PROSPERO platform under registration ID number CRD42020202896. A survey was done on the main databases and in the platform itself, to which this study was submitted and registered. Systematic reviews with the same objective were not found and, therefore, to our knowledge, this study is considered not only relevant, but unprecedented.

2.1 CLINICAL QUESTIONS

What are the impacts of alcohol consumption during pregnancy in relation to fetal craniofacial development?

Can alcohol ingested by the mother during pregnancy be a source of facial anomalies in the fetus?

2.2 PECO STATEMENT

The PECO statement (UNIVERSITY LIBRARY, 2019) used was the one described below:

P - Patients, problem or population: human fetuses or embryos exposed to alcohol during their fetal or embryonic development;

E - Exposure: alcohol consumption by pregnant women;

C - Comparison: pregnant women who abstain from alcohol consumption;

O - Outcome: fetal craniofacial (de)formation.

2.3 PROTOCOL USED

This systematic review followed the guidelines “Meta-analysis Of Observational Studies in Epidemiology” (MOOSE), (Stroup *et al.*, 2000).

2.4 ELIGIBILITY CRITERIA

Observational prospective analytical studies - cohort, observational analytical - cross-sectional studies, observational analytical studies - case-control and observational analytical studies - case series describing or reporting the effects of alcohol on fetal craniofacial development were included. Literature reviews, book chapters, consensus, manuals, and editorials were excluded.

2.5 SEARCH STRATEGY

As a tool for research strategy, several electronic databases were used. The authors chose seven platforms: Pubmed, Lilacs, MedLine, Scopus, Science Direct, Web of Science and Google Scholar and used the following combination of terms for each database, and the last search was carried out in 2019 November (Table 1).

Two independent researchers performed the systematic search and evaluated the summaries of the 278 studies found (116 studies in humans and 162 studies in animals). Any possible disagreement was resolved by a third researcher.

Table 1. Search strategy in various electronic database.

Electronic Database	Search Strategy
Pubmed, **Scopus** and **Web of Science**	((pregnancy) OR (pregnancies) OR (gestation) OR (prenatal care) OR (maternal-fetal relations)) AND ((FASD) OR (Partial Fetal Alcohol Syndrome) OR (Alcohol Related Birth Defects) OR (Birth Defects) OR (Alcohol-Related) OR (Growth Retardation) OR (Facial Abnormalities) OR (Central Nervous System Dysfunction) OR (FAE) OR (Fetal Alcohol Effects) OR (Syndrome) OR (Spectrum Disorders)) AND ((Abnormalities) OR (Anomalies) OR (Malformations) OR (Defects) OR (Deformities) OR (((Congenital) OR (Birth)) AND (defects)) AND ((Fetal) AND ((Development) OR (Growth))) AND ((Alcohol) OR (Ethanol) OR ((Alcoholic) AND (Beverage))) AND (((Craniofacial) AND ((growth) OR (development) OR (morphology)))
Lilacs and **Medline**	((Gravidez) OR (Pregnancy) OR (Embarazo) OR (Gestação) OR (Gestation) OR (Gestación)) AND ((Malformações) OR (Malformations) OR (Malformaciones) OR (Defeitos) OR (Defects) OR (Defectos)) AND ((Álcool) OR (Alcohol) OR (Etanol) OR (Ethanol)) AND ((Craniofacial) OR (Craneofacial))
ScienceDirect	((Pregnancy) OR (Gestation)) AND ((Malformations) OR (Defects)) AND ((Alcohol) OR (Ethanol) OR (Alcoholic Beverage) OR (Alcoholic Beverages)) AND (Craniofacial)
Google Scholar	((Pregnancy) OR (Gestation)) AND ((Malformations) OR (Defects)) AND ((Fetal Development)) AND ((Alcohol) OR (Ethanol) OR (Alcoholic Beverage) OR (Alcoholic Beverages)) AND ((Craniofacial Development) OR (Craniofacial))

2.6 DATA EXTRACTION

The selected studies have been evaluated under the recommendations of Grading of Recommendations, Assessment, Development and Evaluations (GRADE) which the authors performed the evaluation of Risk of bias, Imprecision, Inconsistency, Indirectness and Publication bias with the classification of very low, low, moderate, and high ratings into the studies. We also appraised the same studies with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) instrument to highlight weaknesses in the included studies and to facilitate critical assessment and interpretation of results.

All studies included by the eligibility criteria were processed for data extraction by two researchers who separated them according to the standardized protocol, in this case, by author, year of publication, type of study, sample (N sample and N control), gestational period of alcohol exposure (embryonic or fetal), alcohol concentration (dose), follow-up period, diagnostic instrument and observed alterations.

3 RESULTS

3.1 CHARACTERISTICS OF THE INCLUDED STUDIES

Previously a total of 278 were identified in above mentioned databases. After screening and analysis based on the inclusion criteria, twenty-six observational studies in humans were chosen for the configuration of this systematic review. Of the twenty-six studies included in this systematic review, eight were observational analytical cohort studies, ten were observational analytical sectional studies, six were observational analytical case-control studies, and two were observational descriptive case series studies (Tables 2-5).

3.2 QUALITY ASSESSMENT

All included studies were submitted to quality assessment based on the GRADE and STROBE evaluation as shown in the supplementary material (Table 6-9) .

Among the included studies, six had very low quality of evidence rating, three had low quality, four had moderate quality, and thirteen were rated as high quality of evidence.

Participant eligibility criteria were correctly described in five cohort studies (Olsen and Tuntiseranee, 1995; Kuehn *et a.l*, 2021; Ernhart *et a.l*, 1987; Rostand *et al.*, 1990; Muggli *et al.*, 2017), in five case-control studies (Falagan-Lotsch *et al.*, 2015; Gir *et a.l*, 1989; Hug *et a.l*, 2000; Zarante *et al.*, 2009; Tanaka *et a.l*, 1981), and in ten of the cross-sectional studies (Jones *et al.*, 1973; Ervalahti *et al.*, 2007; Moore *et al.*, 2001; Moore *et al.*, 2002; Robertson *et al.*, 2015; Frias *et a.l*, 1982; Klingenberg *et al.*, 2010; Mutsvangwa *et a.l*, 2009; Naidoo *et al.*, 2006a; Naidoo *et al.*, 2006b). Three cross-sectional studies (Jones *et al.*, 1973; Naidoo *et al.*, 2006a; Naidoo *et al.*, 2006b) and three case-control studies (Hug *et al.*, 2000; Munger *et al.*, 1996; Tanaka *et al.*, 1981) did not explain their criteria for determining sample size, and the tools used to measure alcohol exposure were not clear in eighteen articles (Falangan-Lotsch *et al.*, 2015; Gir *et a.l*, 1989; Hug *et al.*, 2000; Munger *et al.*, 1996; Zarante *et al.*, 2009; Tanaka *et al.*, 1981; Frias *et*

al., 1982; Johnson *et al.*, 1996; Klingenberg *et al.*, 2010; Mutsvangwa *et al.*, 2009; Naidoo *et al.*, 2006a; Naidoo *et al.*, 2006b; Ervalahti *et al.*, 2007; Jones *et a.l*, 1973; Moore *et a.l*, 2001; Moore *et al.*, 2002; Spohr *et a.l*, 2007; Ernhart *et al.*, 1987). Two of the case-control studies performed case-control matching (Falangan-Lotsch *et al.*, 2015; Munger *et al.*, 1996).

In addition, six studies (Rostand *et al.*, 2014; Hug *et al.*, 2000; Tanaka *et al.*, 1981; Frias *et al.*, 1982; Johnson *et al.*, 1996; Mutsvangwa *et al.*, 2009) did not use statistical methods and seven (Olsen *et a.l*, 1995; Ervalahti *et al.*, 2007; Moore *et a.l*, 2001; Moore *et al.*, 2002; Falangan-Lotsch *et al.*, 2015; Gir *et a.l*, 1989; Klingenberg *et al.*, 2010) did not describe the statistical method used to examine the subgroups and associations. However, seven (Olsen *et al.*, 1995; Ernhart *et al.*, 1987; Rostand *et al.*, 2014; Muggli *et al.*, 2017; Gir *et al.*, 1989; Munger *et al.*, 1996; Zarante *et a.l*, 2009) described the measures adopted to avoid confusion.

A total of three studies considered cleft lip and palate as outcomes of interest (Johnson *et al*, 1996; Falangan-Lotsch *et al.*, 2015; Munger *et al.*, 1996), while six considered head circumference and low birth weight (Escobar *et al.*, 1993; Spohr *et a.l*, 2007; Jones *et a.l*, 2009; Gir *et al.*, 1989; Tanaka *et a.l*, 1981; Mutsvangwa *et al.*, 2009), seven identified the presence of FAS (Spohr *et al.*, 2007; Escobar *et al.*, 1993; Ervalahti *et a.l*, 2007; Jones *et al.*, 2009; Hug *et al.*, 2000; Tanaka *et al.*, 1981; Mutsvangwa *et al.*, 2009), and other studies considered minor anomalies such as microcephaly, a poorly developed nasal bone and a thin upper lip (Autti-Rämö *et al.*, 1992; Olsen *et al.*, 1995; Kuehn *et al.*, 2012; Ernhart *et al.*, 1987; Rostand *et al.*, 2014; Muggli *et al.*, 2017; Frias *et al.*, 1982; Klingenberg *et al.*, 2010; Moore *et al.*, 2001; Moore *et al.*, 2002; Robertson *et al.*, 2015; Naidoo *et al.*, 2006a; Naidoo *et al.*, 2006b; Zarante *et al.*, 2009).

Of the cohort studies, eight (Autti-Rämö *et al.*, 1992; Escobar *et al.*, 1993; Olsen *et al.*, 1995; Kuehn *et al.*, 2012; Spohr *et al.*, 2007; Ernhart *et al.*, 1987; Rostand *et al.*, 2014; Muggli *et al.*, 2017) presented the follow-up period (mean and total time), and the main outcomes were described in all studies. Notably, sixteen studies (Autti-Rämö *et al.*, 1992; Escobar *et al.*, 1993; Olsen *et al.*, 1995; Kuehn *et al.*, 2012; Spohr *et al.*, 2007; Ernhart *et a.l*, 1987; Rostand *et al.*, 2014; Muggli *et al.*, 2017; Ervalahti *et al.*, 2007; Moore *et al.*, 2001; Moore *et al.*, 2002; Robertson *et al.*, 2015; Falangan-Lotsch *et al.*, 2015; Munger *et al.*, 1996; Klingenberg *et al.*, 2010; Mutsvangwa *et al.*, 2009) described the limitations and their respective implications in the Discussion section.

Figure 1. Flow Diagram for identification, screening, eligibility, and analysis of studies in humans included in this current systematic review.

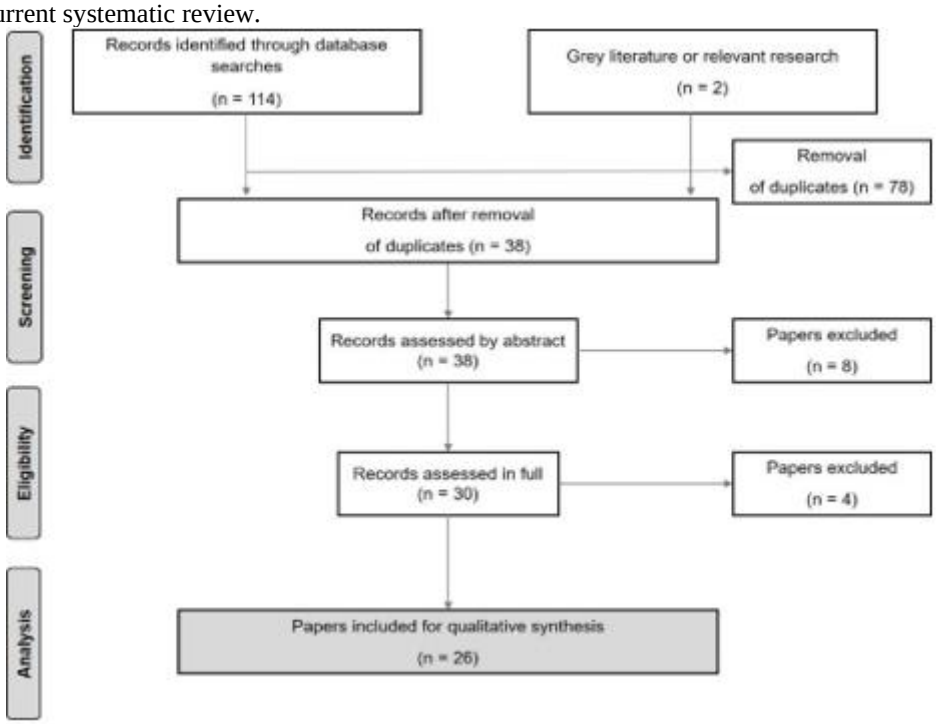

Table 2. Prospective analytical observational studies – cohort.

First author (Year)	Study	Sample		Gestational period	Dosage[3]	Follow-up after birth	Diagnostic instrument	Developmental alterations observed
		E[1]	C[2]					
Autti-Ramo *et al.*, (1992)	Prospective analytical observational studies - cohort	52	48	Embryonic; fetal	1.5	12 months	Clinical evaluation (pattern of facial dysmorphologies proposed by Smith et al., 1988).	Minor physical anomalies; facial features typical of presence of FAS; FAE
Escobar *et al.*, (1993)		5	-	Fetal	2; more than 2	One clinical examination after birth	Prenatal cephalometric analysis by ultrasound	Presence of FAS, FAE, Crouzon syndrome and thanatophoric dysplasia
Olsen and Tuntiseranee (1995)		164	-	Embryonic; fetal	0.7	18 months	Self-reported alcohol intake; photographic register	Association between excessive alcohol consumption and short eyelid cleft
Kuehn *et al.*, (2012)		92	97	Embryonic; fetal	3	8.5 years	Clinical evaluation with blinding of the evaluator	One or more central nervous system functional abnormalities; growth restriction; abnormal facial features
Rostand *et al.*, (2014)		202	-	Embryonic; fetal	0 to 0.8; 1 to 2.8; 3 or more	One week	Standardized morphological examination	Babies born to alcoholics had a higher frequency of craniofacial anomalies and a higher proportion of characteristics compatible with FAE
Spohr *et al.*, (2007)		37	-	-	-	20 years	Clinical evaluation; psychosocial interviews; behavioral checklist	Microcephaly, poorly developed nasal bone and thin upper lip; to a lesser extent, short stature and low weight (in boys) persisting even into adulthood; persistent mental disabilities, including intellectual disabilities, limited occupational options and a dependent lifestyle
Ernhart *et al.*, (1987)		359	183	Embryonic; fetal	More than 6	28 days	Standardized neonatal evaluation; examinations using multivariate techniques	Dose-response relationship between craniofacial abnormalities and prenatal alcohol exposure; the critical period for the alcohol teratogenicity was confirmed around the conception period
Muggli *et al.*, (2017)		46	-	Embryonic; fetal	-	12 months	Three-dimensional craniofacial images obtained at 12 months of life; objective holistic craniofacial phenotyping using dense surface models of face and head	Anatomical differences in the craniofacial form; association between craniofacial form and prenatal alcohol exposure at any level; higher frequency of abnormalities in the middle of the face, nose, lips and eyes, including middle face general recession and nose upper displacement, which indicates nose shortening

Table 3. Analytical observational – cross-sectional studies.

First author (Year)	Study	Exposure sample (n)	Control sample (n)	Diagnostic instrument	Developmental alterations observed
Ervalahti *et al.*, (2007)	Analytical observational studies – cross-sectional	48	-	Clinical evaluation (pattern of facial dysmorphologies); cognitive ability evaluation	Significant correlation between TDS and cognitive ability; correlation between length and weight measures at birth and general cognitive capacity; correlation between head circumference and performance IQ
Frias *et al.*, (1982)		12	47	Cephalometric radiograph	Medium-facial deficiency
Jones *et al.*, (2009)		545	385	Structured protocol to assess specific FAS dysmorphologies; rigid ruler and measuring tape to measure PFL and OFC, respectively	Among all children with FAS, only 10.2% of PFL dysmorphologies can be explained by OFC; 89.8% of PFL dysmorphologies occurs due to factors other than OFC
Klingenberg *et al.*, (2010)		-	-	Facial scans to obtain data on the relative position of 17 morphological landmarks	Significant facial shape directional asymmetry, displacement of reference points from the midline to the right and a displacement of reference points araound the eyes to the left; greater mean directional asymmetry in individuals exposed to alcohol *in utero*
Moore *et al.*, (2001)		100	31	Craniofacial anthropometric measurements	The step-by-step discriminant analysis identified 6 craniofacial measures that could differentiate between individuals with and without prenatal alcohol exposure
Moore *et al.*, (2002)		100	31	Craniofacial anthropometric measurements	Pattern of facial anomalies in individuals with FAS; evidence of growth retardation; abnormalities in the neurodevelopment of CNS
Mutsvangwa *et al.*, (2009)		17	17	Generalized procrustean analysis; regression and discriminant function analysis applied to 3D stereophotogrammetric coordinates derived from reference points taken from 34 individuals	Differences in facial shape between individuals with FAS in different age groups were more pronounced than for control subjects
Naidoo *et al.*, (2006a)		90	90	Evaluation of the stage of tooth formation and skeletal age using hand and wrist radiographs	Evidence of a positive association between dental age and skeletal age in both the FAS children and the controls
Robertson *et al.*, (2015)		78		Analysis of the brain using FreeSurfer software	The alcohol dose by occasion was inversely related to cortical thickness in 3 regions – upper parietal lobe, lingual gyrus and post-central gyrus; the effect of prenatal alcohol exposure on performance IQ was mediated by the cortical thickness in the right occipitotemporal region
Naidoo *et al.*, (2006b)		90	90	Lateral cephalometric radiography	FAS children presented with vertically and horizontally underdeveloped maxilla, features of long face syndrome with large gonial angle and a short ramus in relation to total face height; tendency for the development of an anterior open bite, which appears to be compensated for by an increase in the anterior alveolar process to bring the incisor teeth into occlusion

Table 4. Analytical observational studies – case-control.

First author (Year)	Study	Exposure sample (n)	Control sample (n)	Follow-up	Diagnostic instrument	Developmental alterations observed
Falagan-Lotsch *et al.*, (2015)	Analytical observational studies – case-control	218	253	-	Clinical evaluation; genomic analysis (DNA extracted from oral mucosa cells)	Association between the mother's alcohol consumption during pregnancy and the occurrence of fissures
Gir *et al.*, (1989)		15	15	-	Lateral cephalometric radiography	Triad of facial profile diferences: (1) frontal protuberance, (2) palatine plane tilted forward with proclined upper incisors and a acute nasolabial angle acquired from thumbsucking, and (3) length of the mandibular body above average; collectively, they generate the perception of middle face hypoplasia
Zarante *et al.*, (2009)		374	728	5 years	Information collected between 2001 and 2006 in 10 Colombian hospitals	Predominance of craniofacial malformations on the right side, particularly pre-auricular markers, pre-auricular pits and cleft lip with or without palate
Tanaka *et al.*, (1981)		26	-	1 year	Clinical evaluation	Growth failure was found in half of these cases with an increased rate of babies with low birth weight; delayed intelligence, performance IQ scores of 51-75; delayed motor development; craniofacial anomalies, such as nose and hypoplastic filter, narrow lip vermilion and short eyelid fissures, were observed; an aberrant palmar fold was observed with high frequency
Munger *et al.*, (1996)		287	302	4 years	Telephone interviews with the parents of the selected individuals, conducted by the Research Section of the Statistical Laboratory of the Department of Statistics at Iowa State University	Isolated cleft lip palate increased with increasing level of maternal alcohol consumption
Hug *et al.*, (2000)		11	-		Eye evaluation; magnetic resonance imaging; visual acuity test; ERG	Optic nerve hypoplasia in 91% of individuals; visual acuity was reduced in all but one subject; ERG results were abnormal; scotopic ERG was more severely affected than photopic ERG

Table 5. Analytical observational studies – case series.

First author (Year)	Study	Sample (n)	Diagnostic instrument	Developmental alterations observed
Jones and Smith, (1973)	Analytical observational studies – case series	3	Case report	Growth failure, severe cerebral dysmorphogenesis, functional abnormalities and poor joint positioning
Johnson *et al.*, (1996)		9	Magnetic resonance imaging	Agenesis and hypoplasia of the corpus callosum, ventriculomegaly, hypoplasia of the lower olivary eminences, small brainstem and microcephaly; craniofacial anomalies range from the well-recognized FAS physiognomy to the most severe frontonasal "dysplasia" (median cleft of the face); abnormalities of the central nervous system and craniofacials are predominantly symmetrical and in the central or midline

Table 6. Grade evidence profile for quality assessment of evidence from the included studies (prospective observational cohort) in this current systematic review.

Study	Limitation	Inconsistency	Indirectness	Imprecision	Risk of bias	Quality grading
Autti-Ramo *et al.*, (1992)	No serious limitation	No serious inconsistency	Low level of indirectness	Low level of imprecision	No serious risk of bias	□□□□ High
Escobar *et al.*, (1993)	Serious limitation refereed to the number of included sample (sample size smaller than the required for the statistical measure)	Serious inconsistency – The number of sample size was not mentioned in the material and methods but is informed in the results, only	No serious level of indirectness	No serious imprecision	Serious risk of bias for the non-inclusion of details on the methodological aspects	□○○○ Very low
Olsen and Tuntiseranee (1995)	No serious limitation	No serious inconsistency	No serious indirectness	No serious imprecision	No serious risk of bias	□□□□ High
Kuehn *et al.*, (2012)	No serious limitation	No serious inconsistency	No serious indirectness	No serious imprecision	No serious risk of bias	□□□□ High
Rostand *et al.*, (2014)	No serious limitation	No serious inconsistency	No serious indirectness	No serious imprecision	Serious risk of bias for the non-inclusion of details on the methodological aspects	□□○○ Low
Spohr *et al.*, (2007)	No serious limitation	No serious inconsistency	No serious indirectness	No serious imprecision	No serious risk of bias	□□□□ High
Ernhart *et al.*, (1987)	No serious limitation	No serious inconsistency	Low level of indirectness	Low level of imprecision	No serious risk of bias	□□□□ High
Muggli *et al.*, (2017)	No serious limitation	No serious inconsistency	No serious indirectness	No serious imprecision	No serious risk of bias	□□□□ High

Table 7. Grade evidence profile for quality assessment of evidence from the included studies (cross-sectional studies) in this current systematic review.

Study	Limitation	Inconsistency	Indirectness	Imprecision	Risk of bias	Quality grading
Ervalahti *et al.*, (2007)	Low level of limitation related to the decreased sample size	No serious inconsistency	Low level of indirectness	Low level of imprecision	No serious risk of bias	□□□○ Moderate
Frias *et al.*, (1982)	No serious limitation	No serious inconsistency	No serious level of indirectness	No serious imprecision	Serious risk of bias for the non-inclusion of details on the methodological aspects	□□○○ Low
Jones *et al.*, (2009)	No serious limitation	No serious inconsistency	Low level of indirectness	Low level of imprecision	No serious risk of bias	□□□○ Moderate
Klingenberg *et al.*, (2010)	No serious limitation	No serious inconsistency	Low level of indirectness	Low level of imprecision	No serious risk of bias	□□□○ Moderate
Moore *et al.*, (2001)	No serious limitation	No serious inconsistency	No serious indirectness	No serious imprecision	No serious risk of bias	□□□□ High
Moore *et al.*, (2002)	Serious evidence of limitation (Similar data for previous study)	Serious inconsistency (Similar data for previous study)	No serious indirectness	No serious imprecision	Serious risk of bias (Similar data for previous study)	□○○○ Very low
Mutsvangwa *et al.*, (2009)	Serious limitation refereed to the number of included sample (sample size smaller than the required for the statistical measure)	No serious inconsistency	No serious indirectness	Low level of imprecision	No serious risk of bias	□□○○ Low
Naidoo *et al.*, (2006a)	No serious limitation	No serious inconsistency	No serious indirectness	No serious imprecision	No serious risk of bias	□□□□ High
Robertson *et al.*, (2015)	No serious limitation	No serious inconsistency	No serious indirectness	No serious imprecision	No serious risk of bias	□□□□ High
Naidoo *et al.*, (2006b)	Serious evidence of limitation (Similar data for previous study)	Serious inconsistency (Similar data for previous study)	No serious indirectness	No serious imprecision	Serious risk of bias (Similar data for previous study)	□○○○ Very low

Table 8. Grade evidence profile for quality assessment of evidence from the included studies (case-control studies) in this current systematic review.

Study	Limitation	Inconsistency	Indirectness	Imprecision	Risk of bias	Quality grading
Falagan-Lotsch *et al.*, (2015)	No serious limitation	No serious inconsistency	No serious indirectness	No serious imprecision	No serious risk of bias	□□□□ High
Gir *et al.*, (1989)	No serious limitation	No serious inconsistency	Low level of indirectness	Low level of imprecision	No serious risk of bias	□□□□ High
Zarante *et al.*, (2009)	No serious limitation	No serious inconsistency	No serious indirectness	No serious imprecision	No serious risk of bias	□□□□ High
Tanaka *et al.*, (1981)	Serious limitation refereed to the number of included sample (sample size smaller than the required for the statistical measure)	No serious inconsistency	No serious indirectness	No serious imprecision	No serious risk of bias	□□□○ Moderate
Munger *et al.*, (1996)	No serious limitation	No serious inconsistency	Low level of indirectness	Low level of imprecision	No serious risk of bias	□□□□ High
Hug *et al.*, (2000)	Serious limitation refereed to the number of included sample (sample size smaller than the required for the statistical measure)	No serious inconsistency	No serious level of indirectness	No serious imprecision	Serious risk of bias for the non-inclusion of details on the methodological aspects	□○○○ Very low

Table 9. Grade evidence profile for quality assessment of evidence from the included studies (case series) in this current systematic review.

Study	Limitation	Inconsistency	Indirectness	Imprecision	Risk of bias	Quality grading
Jones and Smith, (1973)	Serious limitation refereed to the number of included sample (sample size smaller than the required for the statistical measure)	Serious inconsistency – The number of sample size was not mentioned in the material and methods but is informed in the results, only	No serious level of indirectness	No serious imprecision	Serious risk of bias for the non-inclusion of details on the methodological aspects	□○○○ Very low
Johnson *et al.*, (1996)	Serious limitation refereed to the number of included sample (sample size smaller than the required for the statistical measure)	Serious inconsistency – The number of sample size was not mentioned in the material and methods but is informed in the results, only	No serious level of indirectness	No serious imprecision	Serious risk of bias for the non-inclusion of details on the methodological aspects	□○○○ Very low

4 DISCUSSION

This systematic review synthesizes data on the effects of alcohol ingested by pregnant women with regard to the craniofacial development of the embryo or fetus. Alcohol intake during pregnancy directly affects embryonic and fetal development (Caputo *et al.,* 2016), which can result in premature birth (Ervalahti *et al.,* 2007), abnormalities within the heart, kidney, liver, gastrointestinal tract, and the endocrine systems (CAPUTO *et al,* 2016). Observable aftereffects vary between growth restriction, distinct craniofacial anomalies, and central nervous system dysfunction, among other alterations (Ervalahti *et al.,* 2007). Caputo *et al.,* (2016) evidenced that in prenatal alcohol consumption the brain was the most severe damage organ. Zhang *et al.,* (2020) in their systematic review study indicates that parental alcohol exposures are significantly associated with the risk of congenital heart disease in offspring.

In a study of 100 children exposed or unexposed to alcohol, a significantly higher number of small physical abnormalities was observed in children of the group exposed to alcohol in the prenatal period. Excessive alcohol consumption was not associated with an increase in the number of these abnormalities, which supports the idea that craniofacial abnormalities are not related to alcohol exposure in a dose-response form (Autti-Rämö *et al.,* 1992) (Table 2). On the other hand, data from a cohort of 359 neonates from a large prospective observational study showed that the levels of craniofacial abnormalities differed according to the dose and period of alcohol intake by the mother. The critical period for alcohol teratogenicity was confirmed around the time of conception. On the other hand, because of a tendency towards an increase in craniofacial abnormalities with increased embryonic exposure to alcohol at lower levels, a clear limit could not be defined (Ernhart *et al.*, 1987), (Table 2).

Kuehn *et al.,* (2012), in their prospective cohort study, concluded that after excessive exposure to alcohol during pregnancy, 80% of the children had one or more abnormalities associated with excessive alcohol consumption, and this was related to a high total weekly consumption (Table 2).

Despite the dose-response relationship and the critical period of exposure to alcohol being defined by Ernhart *et al.*, (1987), a consistent association between craniofacial form and prenatal alcohol exposure was observed at almost any level, regardless of whether exposure occurred only in the first trimester or throughout pregnancy. The regions of anatomical differences in global and regional craniofacial form between children of women who abstained from alcohol during pregnancy and children

with varying levels of prenatal alcohol exposure were concentrated around the middle face, nose, lips and eyes. Differences in facial shape between individuals with fetal alcohol syndrome (FAS) in different age groups were more pronounced than for control individuals, supporting the notion that FAS facial abnormalities diminish with age (Muggli *et al.*, 2017); (Table 2).

Although craniofacial malformations that are characteristic of FAS decrease over time, microcephaly, a poorly developed philtrum and a thin upper lip and, to a lesser degree, short stature and low weight (in boys) persist (Spohr *et al.*, 2007). In women, the body weight of adults increases. Persistent mental disabilities, including intellectual disability, limited occupational options, and dependent lifestyle are the main sequelae, and scores for various behavioral problems increase significantly. The devastating effects of intrauterine exposure to alcohol persist into early adulthood and severely limit careers and the possibility of an independent life (Spohr *et al.*, 2007), (Table 2).

Rostand *et al.*, (2014), while analyzing the relationship between the level of alcohol consumption in pregnancy and the craniofacial characteristics of the newborn, found no differences between mothers who were light or moderate drinkers. Even so, babies that are born to alcoholics presented the highest number of craniofacial characteristics compatible with the harmful effects of alcohol. However, babies of mothers who ingested a lot of alcohol, but who reduced consumption due to pregnancy, showed a smaller difference in craniofacial characteristics (Rostand *et al.*, 2014), (Table 2). Autti-Rämö *et al.*, (1992), in their results, emphasized the importance of also recognizing the subtle dysmorphic facial features associated with prenatal alcohol exposure. In the studies of Tanaka *et al.*, (1981), in all 6 accompanied cases, craniofacial anomalies such as hypoplastic nose and philtrum, narrow lip vermilion and short eyelid fissures were observed, although these facial features were also mild (Tanaka *et al.*, 1981) (Table 4). The phenotypic case definition can be used as a screening tool to identify individuals exposed to alcohol in the prenatal period who do not exhibit a “classic” FAS phenotype, but exhibit a more subtle craniofacial dysmorphia (Moore *et al.*, 2002). Autti-Rämö *et al.*, (1992) also concluded that 22 out of 29 (76%) of the exposed children were judged to have typical or possible FAS characteristics during the first year showed signs of central nervous system dysfunction at the age of 27 months. The abnormalities found in a study whose objective was to document the anomalies of the central nervous system in individuals with FAS by magnetic resonance imaging, include agenesis and hypoplasia

of the corpus callosum, ventriculomegaly, hypoplasia of the lower olivary eminences, small brain stem and microcephaly (Johnson *et al.*, 1996) (Table 3).

In search of a relationship between the extent of exposure to alcohol in the uterus with the cortical thickness, it was found that the dose/occasion of alcohol consumption during pregnancy was inversely related to the cortical thickness in 3 different regions – right cuneus/calcarine groove/upper parietal lobe, fusiform gyrus. The effect of prenatal exposure to alcohol on IQ was mediated by cortical thickness in the right occipital-temporal region. It is noteable that a continuous measurement of alcohol consumption by the mother during pregnancy was more sensitive than the diagnosis of FASD (Fetal Alcohol Spectrum Disorder) and that the effect on cortical thickness was more evident in relation to a measurement of excessive alcohol consumption by the mother (Robertson *et al.*, 2016) (Table 3).

With the clarification of the occurrence of CNS disorders, the relationship between dysmorphic characteristics and general cognitive ability were analyzed by Ervalahti *et al.*, (2007) in a study with Finnish children with FASD. The results showed a significant correlation between total dysmorphology score (TDS) and cognitive ability, suggesting that children with more severe growth impairment and dysmorphic characteristics have more cognitive limitations. Measurements of length and weight at birth also correlated with overall cognitive ability. Head circumference correlated only with performance IQ. These findings imply an inverse relationship between growth deficiency/dysmorphic characteristics and cognitive function in children with FASD (Ervalahti *et al.*, 2007) (Table 3). The same occurred in the study by Tanaka *et al.*, (1981), in which growth deficiency was found in half of cases, with an increased rate of babies with low birth weight (42% of cases), including small full term babies (23% of cases). More than 90% of these cases were in the delayed intelligence group, 50% of which had IQ scores of 51-75. Gross motor coordination development was also delayed (Tanaka *et al.*, 1981) (Table 4).

Another association made with alcohol consumption during pregnancy was with the occurrence of non-syndromic oral clefts. The potential effect that alcohol intake by the mother has on the risk of oral clefts was confirmed in a population of 218 patients in a study conducted in 2015 (Falagan-Lotsch *et al.*, 2015) (Table 4). The study by Munger *et al.*, (1996) showed similar results, stating that compared to women who did not drink alcohol during pregnancy, the relative chances of cleft lip increased with increased maternal alcohol consumption level. With this, it can be said that the consumption of

alcohol during pregnancy can be a cause of isolated cleft lip with or without cleft palate (Munger *et al.*, 1996) (Table 4).

Frias *et al.*, (1982), in their study, observed that mid-facial deficiency is not caused by true maxillary hypoplasia, as some other studies thought, but rather by retrusion of the maxilla. They also stated that this abnormal position is secondary to restricted anterior growth of the face, resulting from abnormal growth of the brain and subsequent shortening of the anterior base of the skull (Frias *et al.*, 1982) (Table 3).

A triad of facial profile differences can also be noted by patients with fetal alcohol syndrome, such as (1) frontal bulge, (2) forward-leaning palatine plane with proclinated upper incisors and an acute nasolabial angle acquired from thumbsucking, and (3) above-average length of the mandibular body. Collectively these generate the *perception* of midface hypoplasia, although the midface actually is unremarkable in size and position (Gir *et al.*, 1989) (Table 4). Another triad also brought mid-facial hypoplasia to the fore by stating that the FAS face is classically characterized by small eyelid fissures, a thin upper lip and mid-facial hypoplasia (Mutsvangwa *et al.*, 2010) (Table 3). In addition, another point raised was that CNS and craniofacial abnormalities are predominantly symmetrical in the center or middle line. The association of these anomalies becomes evident with the recognition of the concept of the midline as a special field of development, vulnerable to adverse factors during embryogenesis, growth and fetal development (Johnson *et al.*, 1996)

Other analyses showed significant directional asymmetry of the facial shape, consisting mainly of a shift of the midline reference points to the right and a shift of the reference points around the eyes to the left. The asymmetry of the FAS and control groups differed significantly, and the mean directional asymmetry was increased in individuals exposed to alcohol *in utero* (Klingenberg *et al.*, 2009) (Table 3). Measurements related to facial height and jaw size appear to be the most important characteristics in distinguishing children with FAS (Naidoo *et al.*, 2006b) (Table 3).

Another interesting finding concerns ophthalmology as another possible area of diagnosis of FAS, since prenatal exposure to alcohol has shown that it can lead to changes in retinal function, as evidenced by an abnormal electroretinogram (ERG) response. ERG can therefore be a tool to identify suspected alcohol embryopathy (Hug *et al.*, 2000) (Table 4).

Although the studies included in this systematic review are quite consistent, due to a lack of standardization in these studies with regard to sample size, types of analyses

performed and length of follow-up of patients, it has become difficult to perform a meta-analysis, as well as making it difficult to establish relationships between the data. Caputo *et al.*, (2016), also mention the importance of standardization of the studies with more specific and accurate measures for identifying when in gestational period the alcohol consumption induces more fetal damages.

The presence of memory bias in studies that made use of questionnaires or interviews makes these studies become very dependent on the patient's memory regarding the description of the gestational period and the dose of alcohol ingested on occasion. This fact also limits the comparison between each case and the response regarding the period and the safe alcohol dose for pregnant women.

5 CONCLUSION

Based on the above analysis, it is evident the impact of maternal alcohol consumption on fetal craniofacial development and that these complications can be harmful to the patient's quality of life, both in childhood and in adulthood, and cause lifelong sequelae. The results also suggest that in order to completely avoid craniofacial anatomical abnormalities related to alcohol, the best advice is to stop alcohol consumption or at least reduce it to a minimum level before conception.

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