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INTELLIGENCE AND FETAL ALCOHOL SPECTRUM DISORDERS: A REVIEW

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ABSTRACT

Background:
The studies on intelligence in individuals with fetal alcohol exposure are conflicting. Some have found a relevant impairment in this population, while others found results that were consistent with the population at large.

Objectives:
Describe the results of studies on intelligence in individuals with Fetal Alcohol Spectrum Disorders.

Methods:
Indexed articles of the last 10 years were selected for an integrative literature review. After inclusion and exclusion criteria were satisfied 37 articles were selected.

Results:
General intelligence, both verbal and non-verbal, is impaired in people who are prenatally exposed to alcohol. There is a tendency to a greater reduction in the Freedom from Distractibility/Working Memory Index of Wechsler Scales.

Conclusions:
Reduction in intelligence seems to occur on a continuum similar to the fetal alcohol spectrum. The reduction of the Freedom from Distractibility/Working Memory Index appears to be a reflection of a greater impairment of mathematical ability.

Key Words: *Fetal Alcohol Spectrum Disorders, Fetal Alcohol Syndrome, Intellectual Functioning, Intelligence, Prenatal Alcohol Exposure*

Individuals suffering from prenatal exposure to alcohol may have disorders from prenatal and postnatal growth (reduced height and/or weight), a specific pattern of facial malformation (short palpebral fissures, thin lips, smooth *philtrum*), and disorders of the central nervous system (neural, structural and/or functional).[1] These features appear on a continuum that ranges from mild to severe. The full spectrum of conditions that can affect individuals who suffered from fetal alcohol exposure is called Fetal Alcohol Spectrum Disorders (FASD) and it covers the following diagnosis[2]:

- Fetal Alcohol Syndrome (FAS). It is the most serious diagnosis, with the complete triad of disabilities in terms of prenatal and postnatal growth, as well as facial and central nervous systems disorders.
- Partial Fetal Alcohol Syndrome (pFAS) incor porates some facial characteristics and other features, or growth or neurodevelopmental disorders.
- Alcohol-related Birth Defects (ARBD) refers to one or more congenital anomalies (cardiac, skeletal, renal, ocular or auditory).
- Alcohol-related Neurodevelopmental Disorder (ARND) refers to neurobehavioural deficits, without physical characteristics and growth retardation.

Currently, the classification of children with fetal alcohol exposure is achieved pursuant to 2 main diagnostic criteria: the Institute of Medicine (IOM) of the National Academy of Sciences (1996 and revised in 2005) and the Washington Criteria, otherwise known as the 4-Digit Diagnostic Code.[2]

The most obvious consequences of fetal alcohol exposure are physical, such as changes in weight, height, head circumference, and facial alterations. However, the most disabling consequences are related to neurobehavioural changes, which include: intellectual deficits, disabilities of executive functions, memory and verbal learning, language and visuospatial skills; delayed motor development; attention deficits; behavioural problems; poor academic performance; adaptive behaviour and emotional difficulties.[3] When health care is inappropriate, fetal alcohol exposure can cause secondary damages that can appear later as legal problems, academic difficulties, dysfunctional behaviour and emotional problems[3]. It is noteworthy that FAS is considered to be one of the major identifiable and non-genetic causes of intellectual disability.[3]

Furthermore, some studies concluded that the intellectual functioning in individuals exposed to alcohol during pregnancy is of average level,[4,5] while others found that most individuals with FASD are not intellectually impaired[3]. No statistically significant effect on intelligence of low to moderate alcohol consumption and episode of binge drinking during gestation was found in a series of studies of a Danish cohort.[6,7] Kesmodel et al.[7] suggest that occasional low alcohol consumption at the beginning and middle of gestation may not cause serious impairment on intellectual functioning.

Before 2006, the reviews have already indicated intellectual impairments in subjects with prenatal alcohol exposure,[8,9] and IQ decrements were related to alcohol exposure. A review of reports revealed that the mean IQ of FAS was between 65 and 75. It was unclear whether verbal IQ was more affected than performance IQ in FAS subjects. However, some studies also found no effects of prenatal alcohol exposure in intellectual functioning.[9]

Thus, while there are studies that have identified impaired intellectual functioning in this population, other studies contradict this. Furthermore, there are few findings regarding the functioning of individuals with FASD in relation to diverse areas of intelligence.

Consequently, the aim of this review article was to identify and describe the results of scientific studies conducted during the last 10 years that investigated intellectual functioning among individuals with FASD. A review of this issue is necessary because of a lack of in-depth information regarding intelligence in this population; most existing revisions unsystematically address cognitive functioning as a whole.

METHODS

The method selected for this study was the integrative literature review. It enables to gather and synthesize various studies published, including those that are experimental and quasi-experimental, in order to draw more comprehensive general conclusions about a particular subject.[10]

Five steps were followed to perform this integrative review: definition of the research question and the research objectives; sample selection; establishment of exclusion and inclusion criteria; literature search; and analysis and categorization of the studies.

The main question addressed by this study was to investigate the results of scientific articles published in indexed journals from January 2006 to May 2016 about intelligence of people with FASD.

On May 22nd, 2016, we searched articles in the following databases: MEDLINE/ PubMed, the Scientific Electronic Library Online (SciELO) and the Web of Science. These databases were chosen because they bring together the top European, North American and Latin American journals. The keywords used for the search in each database is shown in Figure 1.

The inclusion criteria encompassed articles that addressed the issue of intellectual functioning in human beings with FASD or who had been prenatally exposed to alcohol, and which had been published in English or Portuguese during the last 10 years.

The exclusion criteria were: articles that were published before 2006; articles that addressed another issue other than intelligence in humans with FASD or prenatal exposure to alcohol; articles where the full text was unavailable; repeated articles using different keywords and in different bases. In such cases, the articles found after the first search were kept and those that were repeated in subsequent searches were excluded. The flow chart in Figure 1 describes the selection procedures after the inclusion and exclusion criteria were met.

RESULTS

The 37 selected articles were fully read to conduct this integrative review. They were subsequently grouped under the following 3 themes for individuals prenatally exposed to alcohol: general intelligence, verbal and non-verbal intelligence and performance of factorial indexes and subtests of the Weschsler Scales.

The methodological description of these studies is shown in Table 1. The most commonly used

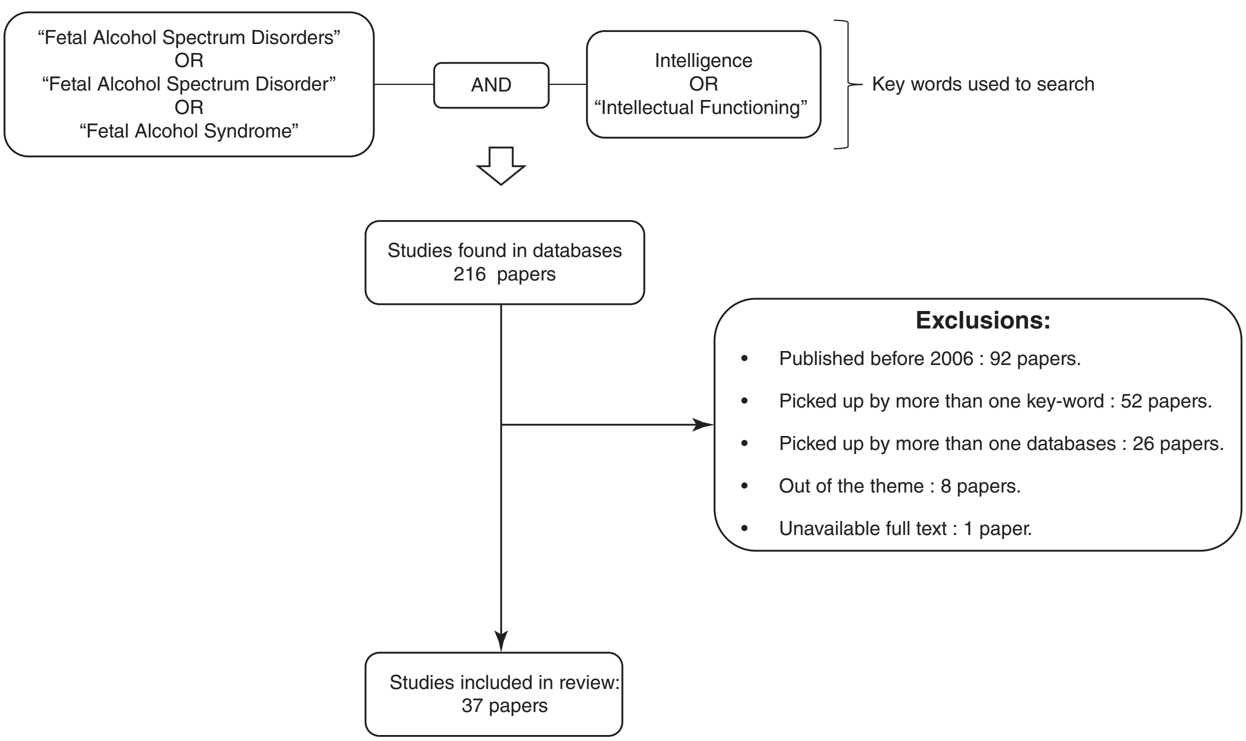

FIG. 1 Flowchart of research.

diagnostic criterion in the studies was the Revised IOM Diagnostic Criteria (43.3% of studies) and most of the samples were collected in the United States (43.3% of the studies).

Theme 1: General Intelligence

A total of 23 studies assessed the overall intelligence of individuals prenatally exposed to alcohol (Table 2). The majority (82.6%) used the Wechsler Scales.

All samples prenatally exposed to alcohol had an IQ (Intelligence Quotient) below 90 in most of the studies (60.9%). Ten studies compared the intellectual performance of individuals exposed to alcohol with the control group. In 90% of them, the group who had been prenatally exposed to alcohol had a global IQ significantly lower than the control group.

Theme 2: Verbal and Non-Verbal Intelligence

Of the 14 studies assessing the verbal and non-verbal intelligence in individuals prenatally exposed to alcohol (Table 2), the majority (64.3%) used the Wechsler Intelligence Scales as an evaluation tool. Studies assessed these individuals as a single group and 71.4% of them found impairments in verbal and non-verbal intelligence (IQ<90 or percentile<25) in at least one of the sampled individuals. Both areas were equally affected.[11,12] Significantly worse performance in both areas were found by 83.3% of the studies in at least one of their samples prenatally exposed to alcohol, compared with the control individuals.

Theme 3: Performance in Relation to Factorial Indexes and Subtests of Wechsler Scale

The results of the Verbal Comprehension Index (VCI), Perceptual Organization/Reasoning Index (POI/ PRI) Freedom from Distractibility/Working Memory Index (FDI/WMI), and Processing Speed Index (PSI) are shown in Table 2.

Nine studies presented the results of factorial indexes of 16 sampled individuals. Half of these samples presented an impairment in all indexes (index <90) and 87.5% of these samples presented this result in at least one index. The VCI and PSI were best preserved in the population prenatally exposed to alcohol. Regarding the VCI, 16.7% of the samples presented an index ≥ 90 and when this parameter was changed to index ≥ 80, this percentage increased to 75%. As for PSI, 28.6% of the samples presented an index ≥ 90 and when this parameter was changed to index ≥ 80, this percentage increased to 71.4%.

However, FDI/ WMI and POI/PRI were most negatively affected in the samples exposed to alcohol. The FDI/WMI <90 was presented by 87.5% and POI/ PRI <90 was presented by 75% of the samples. While comparing and reviewing the results, it was noted that the sample that was prenatally exposed to alcohol was less damaged in terms of VCI[13,14] and POI/PRI.[15]

The PSI results differed between the studies; they were most negatively affected in the population exposed to alcohol as concluded in a study by Dalen et al.[15] and most preserved in a study by Ferreira et al.[19] The FDI/WMI was more adversely affected in the population who were exposed to alcohol[14,15] than other groups. This population significantly underperformed in comparison with other groups.[15,16]

Eight studies provided the results of Wechsler Scales subtests.[15–23] The individuals who were prenatally exposed to alcohol had worse performances in the arithmetic subtest (44.4% of the samples had a scaled score below 6)[16,20,23] and significantly underperformed in relation to the control group as shown in studies by Woods et al.[16] and Gautam et al.[21] Moreover, the samples that were exposed to alcohol showed impaired performance in the comprehension and vocabulary subtests (30% of the exposed samples had a scaled score below 6 in each subtest).[18,20,23]

The performances that were least negatively affected in this population were in the symbol search subtest[15,18,20,21,23] (with 81.8% of the samples exposed to alcohol scoring above 6) and the picture arrangement subtest[15,18,20,21,23] (all samples scored above 6).

Among the studies that compared the performance of children prenatally exposed to alcohol with the control group, in general, individuals with FASD performed worse than the control group in the Wechsler Scales subtests as a whole.[17]

DISCUSSION

This integrative review aimed to present an overview of recent scientific papers published in indexed journals with a focus on the effects of prenatal exposure to alcohol on intellectual functioning. In general, the articles carefully described how the sample was selected and the manner in which the study was

TABLE 1 Methodological Description of the Studies that Made Up the Integrative Review

Authors	Design	Control Group	Blind Examiners	Diagnostic Criteria	Country where data was collected
Aragón et al.(2008b)[11]	Case-control	✓	✓	Revised IOM Diagnostic Criteria.	Italy
Boseck et al. (2014)[12]	Case-control	✓	No information	No information.	USA
Carr, Agnihotri and Keightley (2010)[13]	Case-control	✓	No information	Canadian Guidelines.	Canada
Chasnoff et al.(2010)[14]	Case-control	✓	No information	4-Digit Diagnostic System	USA
Dalen et al. (2009)[15]	Case-control	✓	No information	No information.	Norway
Davis et al.(2013)[16]	Revision	N/A	N/A	N/A	N/A
Ervalahti et al. (2007)[17]	Case-control	✓	✓	Revised IOM Diagnostic Criteria.	Finland
Fernández-Mayoralas et al. (2010)[18]	Series of cases	No	N/A	Canadian Guideline.	Spain
Ferreira et al. (2013)[19]	Series of cases	No	N/A	Children diagnosed by a trained psychiatrist.	Brazil
Foroud et al. (2012)[20]	Cohort	✓	✓	Revised IOM Diagnostic Criteria.	South Africa
Gautam et al. (2015)[21]	Case-control	✓	No information	Revised IOM Diagnostic Criteria.	USA and South Africa
Howell et al. (2006)[22]	Cohort	✓	✓	No information.	USA
Kalberg et al. (2013)[23]	Case-control	✓	✓	Revised IOM Diagnostic Criteria.	South Africa
Kodituwakku (2009)[24]	Revision	N/A	N/A	N/A	N/A
Kodituwakku (2007)[25]	Revision	N/A	N/A	N/A	N/A
Kodituwakku et al. (2006)[26]	Case-control	✓	✓	Revised IOM Diagnostic Criteria.	Italy
Kumada et al.(2007)[27]	Revision	N/A	N/A	N/A	N/A
Lewis et al. (2015)[28]	Cohort	✓	✓	Revised IOM Diagnostic Criteria.	USA and South Africa
May et al. (2013)[29]	Case-control	✓	✓	Revised IOM Diagnostic Criteria.	South Africa
May et al. (2007)[30]	Case-control	✓	✓	Revised IOM Diagnostic Criteria.	South Africa
McGee et al. (2009)[31]	Case-control	✓	✓	Assessment by a dysmorphologist with expertise in teratogenicity of alcohol.	USA

(Continued)

Authors	Design	Control Group	Blind Examiners	Diagnostic Criteria	Country where data was collected
McGee et al. (2008)[32]	Case-control	✓	No information	The children were diagnosed with FAS based on traditional diagnostic criteria.	USA
Meintjes et al. (2014)[33]	Case-control	✓	No information	Revised IOM Diagnostic Criteria.	South Africa
Molteno et al. (2010)[34]	Case-control	✓	✓	Revised IOM Diagnostic Criteria.	South Africa
Nash et al. (2013)[35]	Case-control	✓	No information	Canadian Guidelines and 4-Digit Diagnostic System	Canada
Nash et al. (2008)[36]	Revision	N/A	N/A	N/A	N/A
Nayak et al. (2012)[37]	Case-control	✓	No information	4-Digit Diagnostic System	India
Nuñez, Roussotte and Sowell (2011)[38]	Revision	N/A	N/A	N/A	N/A
Raldiris, Bowers and Towsey (2014)[39]	Case-control	✓	No information	DSM-IV-TR.	USA
Rasmussen, Horne and Witol (2006)[40]	Transversal	No	N/A	4-Digit Diagnostic System	Canada
Schonfeld et al. (2009)[41]	Transversal	No	N/A	4-Digit Diagnostic System	USA
Vaurio, Riley and Mattson (2011)[42]	Case-control	✓	✓	Assessment by a dysmorphologist.	USA
Wacha and Obrzut (2007)[43]	Revision	N/A	N/A	N/A	N/A
Willford, Leech and Day (2006)[44]	Cohort	No	N/A	No information.	USA
Woods et al. (2015)[45]	Case-control	✓	✓	Revised IOM Diagnostic Criteria.	South Africa
Wozniak et al.(2013)[46]	Case-control	✓	No information	4-Digit Diagnostic System and Revised IOM Diagnostic Criteria.	USA
Wozniak et al. (2009)[47]	Case-control	✓	No information	4-Digit Diagnostic System	USA

Legend: N/A: *Not applicable.*

conducted; only a few explained the type of study design. Furthermore, most of the study designs used a control group and/or blind examiners with respect to the sample prenatal alcohol exposure. This may increase the quality of study results.

The use of Revised IOM Diagnostic Criteria in most studies demonstrated a judicious way of diagnosing the samples and a tendency to use a systematic and more easily applicable criteria in clinical routine, as described by Hoyme et al.[2]

TABLE 2 Intellectual Performance of Samples in the Analyzed Studies

Study	Sample	Instrument	Results							Interpretation of Results:
			Overall Intelligence	Non-verbal Intelligence	Verbal Intelligence	VCI	FDI/WMI	POI/PRI	PSI	
Aragón et al.(2008b)[11]	FASD (FAS and pFAS) (n=23)	WISC-R	IQ: 91.3 (15.4)	IQ: 93.7 (16.7)	IQ: 90.9 (14.9)					**Verbal and non-verbal general intelligence**: FASD significantly lower than control.
		Raven's Colored Progressive Matrices		Percentile: 53.0 (26.5)						
	Controls (n=57)	WISC-R	IQ: 107.3 (19.4)	IQ: 111.5 (19.7)	IQ: 101.3 (17.6)					
		Raven's Colored Progressive Matrices		Percentile: 67.4 (22.0)						
Carr, Agnihotri and Keightley (2010)[13]	pFAS (n=12)	WPPSI-III or WISC-IV	IQ: 71.3 (8.4)	IQ: 84.6 (10.9)	IQ: 68.3 (9.3)					**General and verbal intelligence**: no significant difference between the groups. **Non-verbal intelligence**: pFAS significantly lower than ARND and prenatal alcohol exposure.
	ARND (n=14)		Q: 86.7 (13.1)	IQ: 101.2 (14.3)	IQ: 80.6 (14.2)					
	Prenatal alcohol exposure (n=12)		IQ: 81.3 (25.5)	IQ: 97.6 (10.9)	IQ: 75.1 (24.0)					
Chasnoff et al.(2010)[14]	FAS (n=21)	WISC-III				82.2 (15.2)	80.9 (17.4)	78.5 (15.2)	84.0 (17.3)	**Factorial indexes**: FAS significantly lower than pFAS and ARND in all the indexes; pFAS and ARND did not differ between each other.
	pFAS (n=10)					93.3 (7.0)	97.7 (12.0)	92.7 (13.4)	104.4 (16.6)	
	ARND (n=47)					98.8 (15.0)	93.9 (14.4)	96.3 (16.8)	97.6 (17.0)	
Dalen et al. (2009)[15]	FAS (n=29)	WPPSI-R or WISC-R	IQ: 75 (16)	IQ: 77 (16)	IQ: 78 (16)	72 (13.7)	67 (13.9)	71 (17.6)	62 (12.1)	**General and verbal intelligence**: FAS significantly lower than fetal alcohol effects, and the latter was lower than exposure to psychotropic drugs. **Non-verbal intelligence**: FAS significantly lower than the other two groups, who did not differ between each other. **Factorial indexes**: FAS with PSI significantly lower than other factors. Fetal alcohol effects with POI significantly higher, while PSI was significantly lower than the other factors. Exposure to psychotropic drugs, with PSI significantly higher than other factors.
	Fetal alcohol effects (n=35)		IQ: 91 (19)	IQ: 94 (19)	IQ: 91 (18)	85 (16.9)	81 (20.6)	93 (23.0)	74 (13.9)	
	Exposed to psychotropic drugs (n=66)		IQ: 103 (16)	IQ: 101 (16)	IQ: 103 (15)	97 (12.9)	89 (13.2)	94 (17.2)	90 (16.0)	

(Continued)

Study	Sample	Instrument	Results							Interpretation of Results:
			Overall Intelligence	Non-verbal Intelligence	Verbal Intelligence	VCI	FDI/WMI	POI/PRI	PSI	
Ervalahti et al. (2007)[17]	FAS (n=30)	WISC-III	IQ: 70.5 (17.4)	IQ: 69.7 (20.4)	IQ: 72.5 (18.8)					**General and verbal intelligence**: No difference between the groups. **Non-verbal intelligence**: Significant difference between the groups.
	pFAS (n=13)		IQ: 83.8 (16.0)	IQ: 87.3 (16.4)	IQ: 81.5 (19.6)					
	ARND (n=5)		IQ: 78.2 (14.0)	IQ: 75.6 (15.2)	IQ: 81.4 (14.7)					
Fernández-Mayoralas et al. (2010)[18]	FAS, ADHD and Tourette syndrome concomitant (n=9).	WISC-IV and WISC-R	IQ: Case 1) 84; 2) 80; 3) 75; 4) intellectual deficiency; 5) 96; 6) 55; 7) no mental retardation; 8) 80							**General intelligence**: Intellectual disability was confirmed in two cases; the majority showed IQ on the borderline of below average.
		CUMANIN	Case 9) Development quotient: 88							
Ferreira et al. (2013)[19]	Prenatal alcohol exposure (n=10)	WISC-III	IQ: 73.3 (15.9)	IQ: 76.7 (18.8)	IQ: 77.8 (11.8)	81.5 (11.5)	72.8 (8.2)	77.8 (17.3)	84 (16.9)	**General intelligence**: group with an IQ in the borderline range in terms of WISC and in the middle range in relation to Raven's Test. **Verbal and non-verbal intelligence**: No interpretation by the authors. **Factorial indexes**: FDI was the lowest average, followed by POI. VCI and PSI were the least affected indexes.
		Raven's Progressive Matrices Test	Percentile: 28.1 (27.2)							
Foroud et al. (2012)[20]	FAS/pFAS (n=35)	WISC-IV	IQ: 64.7 (10.3) (n=28)							**General intelligence**: FAS/pFAS significantly lower than the other two groups.
		Junior South African Intelligence Scales	IQ: 79.5 (8.0) (n=35)							
	Heavy prenatal alcohol exposure nonsyndromal (n=41)	WISC-IV	IQ: 71.5 (14.9) (n=20)							
		Junior South African Intelligence Scales	IQ: 83.5 (11.2) (n=40)							
	Controls (n=49)	WISC-IV	IQ: 75.9 (12.2) (n=23)							
		Junior South African Intelligence Scales	IQ: 85.6 (9.5) (n=49)							

(Continued)

Study	Sample	Instrument	Results							Interpretation of Results:
			Overall Intelligence	Non-verbal Intelligence	Verbal Intelligence	VCI	FDI/WMI	POI/PRI	PSI	
Howell et al. (2006)[22]	Prenatal alcohol exposure with dysmorphic features (n=46)	WISC-III	IQ: 70.4 (13.9)	IQ: 73.0 (13.7)	IQ: 72.4 (14.2)	73.4 (14.5)	81.8 (13.5)	73.9 (15.3)	81.2 (15.1)	**General intelligence**: all the groups scored in the borderline range. The group that was exposed to alcohol with dysmorphia was significantly lower than the other groups. **Verbal and non-verbal intelligence**: no difference between the groups. **Factorial indexes**: Prenatal alcohol exposure with dysmorphic features significantly lower than the other groups regarding all the indexes except for FDI, which did not present significant difference. The PSI was significantly lower in the groups of prenatal alcohol exposure with dysmorphic features and special education students.
	Prenatal alcohol exposure without dysmorphic features (n=82)		IQ: 78.4 (15.4)	IQ: 79.7 (14.3)	IQ: 80.5 (15.9)	81.0 (16.1)	86.3 (13.4)	79.7 (15.5)	91.8 (12.7)	
	Special education students (n=84)		IQ: 78.4 (14.7)	IQ: 81.6 (15.3)	IQ: 79.6 (14.6)	80.5 (15.7)	81.2 (13.7)	84.1 (15.9)	84.5 (15.3)	
	Controls (n=53)		IQ: 78.4 (10.6)	IQ: 80.0 (11.4)	IQ: 80.3 (10.9)	81.1 (10.8)	85.5 (14.4)	79.5 (11.3)	92.6 (16.2)	
Kalberg et al. (2013)[23]	FASD (n=61)	Raven's Colored Progressive Matrices		Percentile: 13.0 (12.8)						**Non-verbal intelligence**: FASD significantly lower than the control. **Verbal intelligence**: FASD significantly lower in all the tests, except story memory.
		Test of Reception Grammar			Percentile: 6.6 (9.5)					
		Story Memory			Scaled score: 65.9 (18.6)					
		Visual Motor Integration			Standardized Score: 68.0 (12.4)					
	Controls (n=52)	Raven's Colored Progressive Matrices		Percentile: 24.2 (19.5)						
		Test of Reception Grammar			Percentile: 20.3 (20.7)					
		Story Memory			Scaled score: 70.9 (21.8)					
		Visual Motor Integration			Standardized Score: 79.3 (19.3)					

(Continued)

Study	Sample	Instrument	Results							Interpretation of Results:
			Overall Intelligence	Non-verbal Intelligence	Verbal Intelligence	VCI	FDI/WMI	POI/PRI	PSI	
Kodituwakku et al. (2006)[26]	FASD (n=22)	Raven's Colored Progressive Matrices		Percentile: 55 (20.4)						**Non-verbal intelligence**: FASD significantly lower than the control.
	Controls (n=60)			Percentile: 72.5 (20.8)						
Lewis et al. (2015)[28]	Heavy prenatal alcohol exposure (n=91) and non-exposed children (n=60) from Cape Town.	WISC-III and WISC-IV	IQ: 73.4 (13.8)							**General intelligence**: Cape Town sample significantly lower than that of Detroit.
	Moderate-to-heavy prenatal alcohol exposure adolescents from Detroit (n=291).		IQ: 79.0 (13.0)							
May et al. (2013)[29]	FASD (n=185)	Raven's Colored Progressive Matrices		IQ: 83.6 (10.9)						**Verbal and non-verbal intelligence**: no interpretation by the authors.
	Not FASD (n=376)	Test of Reception of Grammar			IQ: 81.0 (13.9)					
May et al. (2007)[30]	FAS (n=55)	Raven's Colored Progressive Matrices		IQ(?): 9.4 (9.1)						**Non-verbal intelligence**: FAS and pFAS significantly lower than the control. **Verbal intelligence**: FAS significantly lower than the control.
		Test of Reception of Grammar			IQ(?): 10.9)					
	pFAS (n=18)	Raven's Colored Progressive Matrices		IQ(?): 10.7 (9.6)						
		Test of Reception of Grammar			IQ(?): 14.0 (15.9)					
	Controls (n=133)	Raven's Colored Progressive Matrices		IQ(?): 21.1 (18.9)						
		Test of Reception of Grammar			IQ(?): 24.1 (21.5)					

(Continued)

Study	Sample	Instrument	Results							Interpretation of Results:
			Overall Intelligence	Non-verbal Intelligence	Verbal Intelligence	VCI	FDI/WMI	POI/PRI	PSI	
McGee et al. (2009)[31]	Heavy prenatal alcohol exposure (n=25)	WPPSI-R and WPPSI-III	IQ: 91.2 (11.5)							**General intelligence**: Exposed group significantly lower than the control.
	Controls (n=26)		IQ: 105.5 (13.6)							
McGee et al. (2008)[32]	Heavy prenatal alcohol exposure (n=47)	WISC-III	IQ: 88.8 (12.2)							**General intelligence**: Exposed group significantly lower than the control.
	Controls (n=60)		IQ: 107.3 (11.6)							
Meintjes et al. (2014)[33]	FAS (n=7)	WISC-IV	IQ: 65.0 (8.7)							**General intelligence**: Exposed groups significantly lower than the control.
	pFAS (n=18)		IQ: 63.6 (10.3)							
	Heavy prenatal alcohol exposure (n=14)		IQ: 72.8 (8.2)							
	Controls (n=16)		IQ: 74.8 (8.1)							
Molteno et al. (2010)[34]	FAS/pFAS (n=29)	Junior South African Intelligence Scales	IQ: 79.0 (8.3)							**General intelligence**: FAS/pFAS significantly lower than the two other groups, which did not differ from each other.
	Heavy prenatal alcohol exposure (n=37)		IQ: 85.9 (11.1)							
	Children of mothers who are light drinkers or abstainers (n=41)		IQ: 84.3 (9.7)							
Nash et al. (2013)[35]	FASD (n=109)	WISC-IV	IQ: 86.9 (11.5)	IQ: 97.2 (8.7)	IQ: 98.6 (8.4)		86.2 (14.3)		89.0 (15.2)	**General intelligence**: FASD significantly lower than the exposed group, but without FASD. **Verbal and non-verbal intelligence and factorial indexes**: no significant difference.
	Prenatal alcohol exposure without FASD (n=61)		IQ: 92.4 (13.8)	IQ: 92.4 (16.4)	IQ: 95.5 (14.1)		87.3 (13.0)		92.1 (18.1)	
Nayak et al. (2012)[37]	Prenatal alcohol exposure (n=26)	Malin's Intelligence Scale for Indian Children	IQ: 72.7 (6.3)	IQ: 67.0 (8.8)	IQ: 78.3 (6.7)					**General, verbal and non-verbal intelligence**: Exposed groups significantly lower than the control.
	Controls (n=27)		IQ: 80.9 (6.4)	IQ: 77.5 (8.3)	IQ: 84.4 (6.7)					
Raldiris, Bowers and Towsey (2014)[39]	FASD (n=25)	WISC-IV	IQ: 75.2 (13.6)			87.0 (11.7)	75.4 (14.4)	79.9 (14.1)	76.0 (14.2)	**General intelligence**: FASD significantly lower than ADHD and other diagnoses. FASD+ADHD did not differ from the FASD and ADHD groups and other diagnoses. **Factorial indexes**: FASD+ADHD significantly lower than VCI when compared to ADHD. FASD significantly lower than PRI, when compared to ADHD group and other diagnoses. FASD significantly lower than WMI when compared to the group and other diagnoses.
	ADHD (n=54)		IQ: 88.2 (14.8)			95.9 (13.9)	84.0 (12.6)	92.9 (13.9)	87.9 (16.1)	
	ADHD+FASD (n=28)		IQ: 79.9 (16.2)			86.6 (15.0)	78.6 (18.4)	86.4 (17.4)	78.7 (13.5)	
	Other diagnosis (n=57)		IQ: 88.2 (16.4)			95.1 (14.7)	87.1 (16.6)	92.5 (15.8)	83.5 (15.8)	

(Continued)

Study	Sample	Instrument	Results							Interpretation of Results:
			Overall Intelligence	Non-verbal Intelligence	Verbal Intelligence	VCI	FDI/WMI	POI/PRI	PSI	
Rasmussen, Horne and Witol (2006)[40]	FASD (n=50)	WISC-III and WPPSI-R	IQ: 80.9 (11.4)	IQ: 87.5 (13.2)	IQ: 78.7 (13.4)					**General intelligence**: FASD with lower than average performance. V**erbal intelligence**: significantly lower than non-verbal intelligence.
Schonfeld et al. (2009)[41]	Prenatal Alcohol Exposure (n=100)	Kaufman Brief Intelligence Test Composite IQ	Composite IQ: 97.2 (14.8)							**General intelligence**: no interpretation by the authors.
Vaurio, Riley and Mattson (2011)[42]	Heavy prenatal alcohol exposure (n=55)	WISC-III	IQ: 92.2 (16.6)	IQ: 94.3 (17.4)	IQ: 91.7 (16.6)					**General, verbal and non-verbal intelligence**: no significant difference.
	IQ-matched comparison group, without prenatal alcohol exposure (n=55)		IQ: 92.6 (16.8)	IQ: 90.8 (16.1)	IQ: 95.5 (18.0)					
Willford, Leech and Day (2006)[44]	Children whose mothers drank 3 or more alcoholic drinks per week and a random sample of women who drank less often, or not at all (n=636).	Stanford-Binet Intelligence Scale, fourth edition	IQ: 91.5 (11.5)							**General intelligence**: Afro-Americans significantly lower than Caucasians.
Woods et al. (2015)[45]	FAS/pFAS (n=18)	WISC-III and WISC-IV	IQ: 59.8 (10.5)				74.4 (16.5)			**General intelligence**: FAS/pFAS significantly lower than the group that was heavily exposed, and the latter was significantly lower than the control. **Factorial indexes**: FAS/pFAS significantly lower than the control in terms of FDI.
	Heavy prenatal alcohol exposure (n=22)		IQ: 67.9 (10.2)				80.6 (10.4)			
	Controls (n=25)		IQ: 76.0 (11.0)				87.4 (12.4)			
Wozniak et al.(2013)[46]	FASD (n=24)	WISC-IV or WAIS-III	IQ: 83 (13.5)			86 (10.9)	85 (17.9)	88 (15.8)	86 (15.8)	**General intelligence**: FASD significantly lower than the control group. **Factorial indexes:** in all the indexes FASD significantly lower than the control.
	Controls (n=31)		IQ: 114 (12.0)			113 (13.2)	108 (12.2)	116 (13.3)	102 (11.9)	

(Continued)

Study	Sample	Instrument	Results							Interpretation of Results:
			Overall Intelligence	Non-verbal Intelligence	Verbal Intelligence	VCI	FDI/WMI	POI/PRI	PSI	
Wozniak et al. (2009)[47]	FASD (n=33)	WISC-IV or WAIS-III	IQ: 76.9 (13.3)			79.5 (11.6)	78.5 (14.8)	84.8 (16.0)	82.0 (14.4)	**General intelligence**: FASD significantly lower than the control group. **Factorial indexes**: in all the indexes FASD significantly lower than the control.
	Controls (n=19)		IQ: 107.3 (11.1)			106.6 (11.5)	102.3 (8.5)	107.4 (12.5)	103.1 (12.1)	

Legend: ADHD: Attention Deficit Hyperactivity Disorder; ARND: Alcohol-related Neurodevelopmental Disorder; CUMANIN: Cuestionario de Madurez Neuropsicológica Infantil [Neuropsychologic Maturity Questionnaire for Children; in Spanish]; FASD: Fetal Alcohol Spectrum Disorder; FAS: Fetal Alcohol Syndrome; FDI/WMI: Freedom from Distractibility/Working Memory Index; IQ: intelligence quotient; pFAS: Partial Fetal Alcohol Syndrome; POI/PRI: Perceptual Organization/Reasoning Index; PSI: Processing Speed Index; VCI: Verbal Comprehension Index; WAIS-III: Wechsler Adult Intelligence Scale – Thrid Edition; WISC-III: Wechsler Intelligence Scale for Children-Thrid Edition; WISC-IV: Wechsler Intelligence Scale for Children-Fourth Edition; WISC-R: Wechsler Intelligence Scale for Children-Revised; WPPSI-III: Wechsler Preschool and Primary Scale of Intelligence-Third Edition; WPPSI-R: Wechsler Preschool and Primary Scale of Intelligence-Revised.

Overall, the articles that assessed intellectual functioning in individuals prenatally exposed to alcohol found general impairment in intelligence.[13,15,16,20,25–34,45] This finding was consistent with the revisions included in this study.[11,12,22,32,38,39]

Curiously, while compiling the studies data, we found that the intellectual performance injury occurs differently depending on the individual diagnosis. This injury appears to come together with the continuum of FASD, FAS being the most adverse diagnosis and with major intellectual impairment, ARND, the least adverse and with better performance and pFAS, the intermediate diagnosis, comprehending a wider spectrum (Figure 2).

These performances shown in Figure 2, were consistent with those described in the literature, in which FAS individuals had a more compromised IQ[22] and individuals with FASD have a performance within the borderline and middle low ranges.[11] However, one clinical sample of a high-quality study was classified in the middle range, possibly due to environmental factors that favoured the cognitive development of children.[17]

When the sampled individuals who were exposed to alcohol were compared with each other, it was found that those with FAS had greater impairment in terms of general,[16,27,31] as well as verbal and non-verbal intelligence.[13] which indicated the most severe form of the spectrum. This information is consistent with the findings of Coriale et al.[3]

Impairments of verbal and non-verbal intelligence in the exposed samples were presented in several studies.[13,20,25,37,41,42] The verbal and non-verbal IQ were equally impaired[38,39] and with an undefined consistent pattern.[36] A study by Nash et al.[32] also highlighted this difficulty in both areas and the same study also

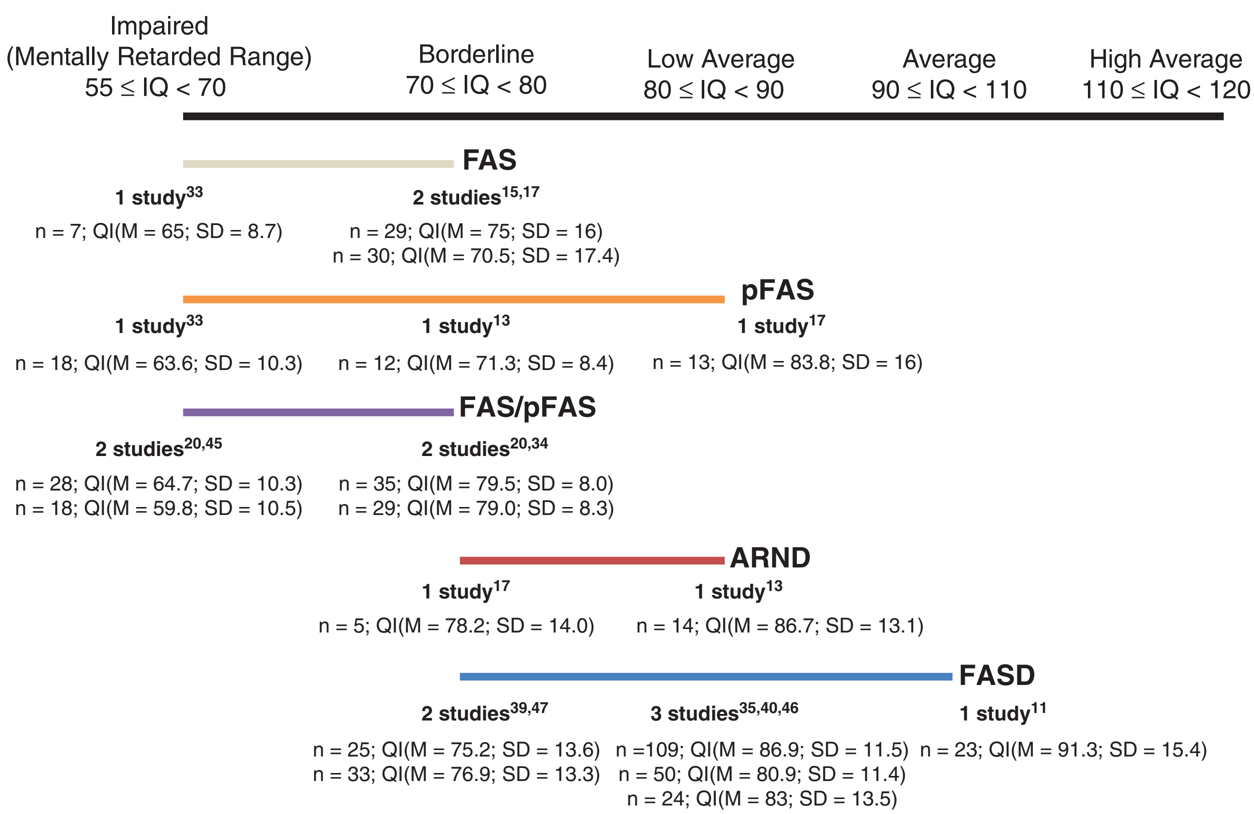

FIG. 2 Graphical representation of intelligence bands and diagnostics of FASD.
ARND = Alcohol-Related Neurodevelopmental Disorder; FASD = Fetal Alcohol Spectrum Disorder; FAS = Fetal Alcohol Syndrome; IQ = Intelligence Quotient; M = mean; N = sample size; pFAS = Partial Fetal Alcohol Syndrome; SD = Standard Deviation.

emphasized that impairment in the verbal domain becomes increasingly pronounced with advancing age.

Regarding the factorial indexes of the Wechsler Scales, the Freedom from Distractibility/Working Memory Index was the most adversely affected, with loss of attention, concentration, immediate memory and mathematical skills.[43]

Concerning the Wechsler Scales subtests, it was noted that there was a predominance of impairment in the arithmetic subtest in the sample that was prenatally exposed to alcohol. This finding is consistent with a publication by Nash et al.[32] According to Cunha,[44] this subtest assesses the "computational capacity and speed in the management of calculations, auditory memory, (...) school experiences, concentration, (...) logical reasoning". Impairment in this subtest implies difficulties in these areas, which may affect academic progress.[32]

The studies that presented some area of intellectual functioning preserved in the sample prenatally exposed to alcohol should be interpreted with caution. Analyzing the samples addressed in these studies, it was clear that mostly they consisted of milder forms of FASD or of individuals who had been exposed to alcohol, but without a diagnosis, as stated in several studies.[13,14,17,20,31,34,35,46,47] The fact that the samples presented predominantly milder forms of FASD resulted in higher scores. This explains why some studies state that most individuals who were prenatally exposed to alcohol are not intellectually impaired.

Moreover, even in clinical samples with more preserved scores, when a control group was used for comparison there was worse performance by the samples prenatally exposed to alcohol in terms of general intelligence,[13,17] verbal intelligence[17] and non-verbal intelligence.[17,26] Consequently, a research that involves case-control is important to demonstrate the actual effect of fetal alcohol exposure.

The high level of cognitive functioning of the clinical sample in a study by Aragón et al[17] may have been due to a stable postnatal environment with high levels of family education, proper nutrition and low unemployment. Furthermore, the majority of individuals in the aforementioned study had pFAS and they were selected from a school, which, unlike a hospital for example, means that they constituted less vulnerable samples. This highlights the socio-environmental influences that could interfere with the intellectual performance of such individuals.

The present integrative review has some limitations, one of which is the fact that the articles that were analyzed used different tests to assess intellectual functioning. As Primi[50] points out, scores from different tests often do not refer exactly to the same capabilities. However, the fact that most studies used the same instrument (WISC) minimized this limitation. It is suggested that subsequent review studies should only select articles that used the same evaluation tool.

Other limitation refers to the samples used in the studies looked for. Our objective was to evaluate the intellectual functioning of individuals with FASD and we used a search strategy for that. Despite this, in our research, we found studies that included participants without the diagnosis, but prenatally exposed to alcohol. This seems to occur due to the difficulty of composing a sample with a significant number of individuals with the same diagnosis, a common complicating factor in fetal alcohol spectrum studies. Consequently, many studies have included children with FASD or with fetal alcohol exposure in a single group and that often results in divergent performance in intellectual functioning. While some samples were composed of individuals with the most severe forms of the spectrum, which results in lower intellectual performances, others samples were composed of individuals with milder forms, with results in better intellectual performances. It may be difficult to gather homogeneous samples and this may be an additional challenge to experimental studies.

We are aware that these 2 samples (FASD and individuals exposed to alcohol at any level) are overlapping, but they are not identical. Despite this, our study contributes to expand knowledge about the consequences of fetal alcohol exposure in various ways.

Moreover, in order to minimize social and cultural interference, multi-centric research is needed because the approach can control factors that possibly influence intellectual functioning (for example, environmental, pattern of alcohol use, etc.), which can overcome the limitations of current results that predominantly focus on North American samples.

The samples of the studies reviewed are heterogeneous, the intelligence assessment instruments are diversified and others uncontrolled environmental factors can influence the results found by these studies. Because it was an integrative review, it was possible to group these studies, based on a more qualitative analysis. However, it is important to say that this type of study is not bias-free. It would be necessary to make efforts to produce systematic reviews and/or meta-analyzes in future studies in order to reduce such problems and increase the quality of evidence presented in this article.

Another limitation of this review was that it was not possible to classify the level of available scientific evidence for the central issue of this study, since this review is not a meta-analysis of ethically acceptable interventions. Future work including meta-analysis of the data obtained can improve the knowledge about this problem.

The review studies that formed part of our integrative review also had limitations. Although they provided relevant information about the cognitive functioning of samples who were prenatally exposed to alcohol, they did not describe the method used for their preparation. Therefore, we emphasize the importance of conducting reviews using various methods so that it is possible to reach conclusions with less biases and greater scientific rigor.

Through this integrative literature review we concluded that general, verbal and non-verbal intelligence are impaired in people who are prenatally exposed to alcohol, and that damage appears to occur in a continuum that is similar to that of fetal alcohol spectrum, with FAS presenting the greatest impairment in all areas of intelligence and ARND presenting the mildest impairment. Furthermore, we noticed that there is a tendency to a greater reduction in results in the Freedom from Distractibility/Working Memory Index. Because this index is obtained by summing 2 subtests (arithmetic and digit span), and because the arithmetic subtest is found to be impaired in this population, it may be that this index is reduced, more specifically because mathematical ability is impaired to a greater degree.

An in-depth focus of this review in terms of intellectual functioning among the population prenatally exposed to alcohol was necessary in order to understand how this difficulty occurs; this information is currently lacking in the review studies that address the issue of cognitive functioning.

Thus, prenatal exposure to alcohol can cause various brain disorders that manifest themselves through changes that are both cognitive, and behavioural. One of these changes is intellectual impairment. A more comprehensive understanding of these changes, by the general population and health professionals can contribute to the prevention of FASD; its early identification and intervention, could seemingly minimize its side effects, such as legal problems, academic difficulties, problems in relationships etc.[3] Prenatal and pediatric care professionals can perform a simple anamnesis if they suspect this syndrome is present. In addition, pregnant women should be advised to refrain from consuming alcohol by professionals in the fields of obstetrics and gynecology. The dissemi nation of this knowledge can contribute to the planning of public policies and can help reduce damage to individuals and society.

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