



Prenatal alcohol use as a risk for attention-deficit/hyperactivity disorder

Daniel Pagnin^{1,2} · Maria Luiza Zamboni Grecco¹ · Erikson Felipe Furtado¹

Received: 29 January 2018 / Accepted: 19 October 2018 / Published online: 23 October 2018
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Abstract

The objective of the study was to investigate the association between alcohol use during pregnancy and mental disorders in childhood, controlling for confounding risk factors by a longitudinal study of pregnant women and their offspring. The initial cohort comprised pregnant women attending an obstetric service. From the initial sample of 449 pregnant women, 81 mother–child pairs agreed to participate. After 12 years, mother–child pairs were assessed through self-administered questionnaires and semi-structured interviews. The Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version (K-SADS-PL) was used to assess the presence of any mental disorders in the children. The mothers were assessed by the Self-Reporting Questionnaire (SRQ) and the Alcohol Use Disorders Identification Test (AUDIT). Furthermore, data on the mother’s alcohol use collected during pregnancy were analysed. A logistic regression tested the influence of alcohol consumption in all trimesters and binge drinking on the occurrence of attention-deficit/hyperactivity disorder (ADHD), controlling for covariates. Binge drinking at any time during pregnancy or low–moderate alcohol consumption in all trimesters of pregnancy was associated with a fivefold increased odds of child ADHD. The combination of both patterns of alcohol use added an increase of 19% in the variance of ADHD’s occurrence. The episodic use of at least four drinks or the regular use of low–moderate alcohol doses during pregnancy was associated with significantly increased odds of subsequent child ADHD. Reducing binge drinking and regular alcohol use of pregnant women may lead to a significant decrease in their children developing ADHD.

Keywords Fetal alcohol spectrum disorders · Attention-deficit/hyperactivity disorder · Disruptive behaviour disorders

Introduction

Alcohol consumption is widespread throughout the world, with the World Health Organization estimating that the global adult population drink on average 6.2 l of pure alcohol per year. More than half of the adult population (52%) have already consumed alcohol in their lifetime [1].

The prevalence of alcohol consumption is lower among women, however, women’s alcohol use has increased as a function of economic development and changing gender roles [1]. Likewise, alcohol use among women of

childbearing age has also increased and consequently, has its use during pregnancy [2–4]. One in ten pregnant women consume alcohol [5], and one in five that do, drink at a level as to risk fetal damage [6], which may result in serious consequences, such as fetal alcohol spectrum disorders (FASD) [7].

At one end of the FASD spectrum, comprehensive fetal alcohol syndrome (FAS) is characterized by facial abnormalities, growth retardation, and central nervous system (CNS) dysfunction; at the other end, more subtle outcomes such as alcohol-related neurodevelopmental disorder (ARND) are characterized by cognitive or behavioural abnormalities [7, 8]. The worldwide prevalence of FAS and ARND are estimated to be 2.89 per 1000 and 5.19 per 1000, respectively [9]. Furthermore, prenatal alcohol exposure can lead to secondary conditions such as mental disorders [10].

Externalizing disorders are common mental disorders in children who were exposed to alcohol during pregnancy. It is estimated that 90.7% and 51.2% of children with FASD

✉ Daniel Pagnin
dpagnin@id.uff.br

¹ Department of Neurosciences and Behavior, University of São Paulo, Ribeirão Preto, São Paulo, Brazil

² Department of Psychiatry and Mental Health, Fluminense Federal University, Rua Marques do Paraná, 303 Prédio Anexo, Niterói, Rio de Janeiro CEP 24030-215, Brazil

suffer from conduct disorder and attention-deficit/hyperactivity disorder (ADHD), respectively [11]. However, the onset of mental disorders can be influenced by moderator and mediator factors, which overlap with independent risk factors [12]. The complex interaction of genetic, metabolic, and nutritional factors [13, 14] have generated uncertainties about the exact role of prenatal risk factors in the onset of mental disorders in childhood [15].

In the case of prenatal alcohol exposure, both the pattern and length of alcohol use are factors to consider. The link between heavy, prolonged use of alcohol and the identifiable characteristics of FAS in newborns is well established. However, the link between low–moderate alcohol consumption and mental disorders in childhood is unclear, and further complicated by the intricate interactions with postnatal environmental factors [16].

Our study assessed the influence of the pattern of alcohol consumption on the occurrence of mental disorders in 12-year-old children exposed to alcohol during pregnancy. In particular, we assessed the episodic and regular use of alcohol as risk factors for ADHD, controlling for the effects of moderator and mediator risk factors.

Methods

This longitudinal prospective study assessed the link between prenatal alcohol exposure and the occurrence of mental disorders in the offspring. The target population was the 12-year-old children of mothers who were assessed in a previous cohort, called *Gesta Alcohol*, in 2001 [17]. This cohort comprised 449 pregnant women who were attending an obstetric service and did not have medical complications. After 12 years, 266 mothers could no longer be found because they had changed city, address or phone number. Of the remaining 183 mothers contacted by phone, 64 refused immediately to participate in the study and 38 did not attend the scheduled interviews. Thus, 81 mother–child pairs participated in a semi-structured psychiatric interview and self-administered questionnaires in the outpatient centre of São Paulo University, Ribeirão Preto city. There were no significant differences between the mothers of the initial sample and those of this study with regard to sociodemographic, alcohol use, and mental health variables [6, 17].

Both the children and mothers voluntarily participated, and the mothers signed informed consent forms for the study. This study was approved by the local research ethics committee.

To assess the occurrence of mental disorders among the children, one of the authors of this study (M.L.Z.G) administered the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version (K-SADS-PL) [18, 19].

The assessment of mental disorders and alcohol consumption in the mother included both the current state and that during the pregnancy. The current maternal assessment included the Self-Reporting Questionnaire (SRQ) [20] to identify any non-psychotic mental disorder, and the Alcohol Use Disorders Identification Test (AUDIT) [21, 22] to identify any potential alcohol problem. The pregnancy assessment included the Adult Psychiatry Morbidity Questionnaire (QMPA) [23] to identify psychiatric morbidity and treatment information; the Tolerance, Annoyed, Cut down and Eye-opener (T-ACE) [6, 24] to identify risk drinking, the ICD-10 criteria to identify harmful use and dependence syndrome, and a questionnaire to identify the occurrence of binge drinking, any alcohol use, number of trimesters of alcohol consumption and alcohol consumption in all trimesters of pregnancy.

Binge drinking in women was defined as the consumption of 4 or more standard drinks within 2 h per episode [25]. A standard drink corresponds approximately to 12 g of alcohol by volume ingested, which means around 330 ml of regular beer, 150 ml of wine or 40 ml of distilled spirits. Low levels of alcohol consumption consisted of less than one drink per day; moderate levels consisted of up to one drink per day. This concept of low–moderate levels considers the amount consumed on any single day, not the mean along several day [26].

Statistical analysis

To summarize the sample characteristics, we used descriptive statistics as frequency and percentage. To compare differences in proportion and chance between groups, we used Pearson Chi-square and calculated odds ratio, respectively. When Pearson Chi-square's assumptions were violated, we used Fisher's exact test or likelihood ratio. Cramer's *V* was used to measure the strength of the association between variables.

Bivariate analyses were made between the presence of children's mental disorders and mother's variables in the current and pregnancy periods. Subsequently, bivariate analyses were performed between these maternal variables and the presence of externalizing, internalizing, and attention-deficit/hyperactivity disorders. Finally, we performed a hierarchical multiple logistic regression to assess the influence of prenatal alcohol exposure on ADHD occurrence, controlling for confounding variables. The assumptions of multiple logistic regression were checked, with potential explanatory variables assessed for collinearity and singularity. Missing values of the independent variables in the regression analysis were replaced by linear interpolation.

Statistical analyses were performed using SPSS 17.0.

Table 1 Mother's demographic, socioeconomic, and family characteristics ($n = 81$)

Characteristics	<i>N</i>	%
Race		
White	40	49.4
Brown	25	30.9
Black	16	19.8
Marital status		
Single/divorced	19	23.5
Married	30	37.0
Widowed	3	3.7
Civil union/partnership	29	35.8
Family income		
Low (extremely poor)	4	4.9
Low (poor)	37	45.7
Middle	32	39.5
High	8	9.9
Attendance at a religious institution		
Non-attendance	22	27.2
Attendance	59	72.8
Schooling		
Without education	1	1.2
Elementary	43	53.1
High school	35	43.2
College	2	2.5
Total number of children		
One	13	16.0
Two	30	37.0
Three	19	19.7
Four	15	18.5
Five	4	4.9
Living with children's father	48	59.3
Family/environmental stressor ^a	16	19.8

^aSerious family disagreement, sudden change on family financial pattern, city change, a first degree relative with criminal charge, death of father or siblings, or serious illness in first degree relative

Results

Sample characteristics

Eighty-one mother–child pairs completed the questionnaires, which resulted in a longitudinal response rate of 18% (81/449). The mean age of mothers during pregnancy was 24.43 (SD 5.12), with a range between 15 and 39 years. Around half of these mothers identified themselves as brown or black, poor, and with elementary education; around three-quarters were religious, and three-quarters married or living with a partner. Most mother–child pairs were living with the child's father, however, one-fifth were facing family or environmental stressors (Table 1). Of the 12-year-old children surveyed, females slightly predominated (56.8%, 46 of 81 respondents).

Regarding the mother's current health, 44.4% (36/81) had medical problems, and 39.5% (32/81) had mental disorders (SRQ). Of those who had mental disorders, 31.2% (10/32) were attending outpatient psychiatric treatment. Likewise, during pregnancy, 33.3% (27/81) had a psychiatric morbidity (QMPA).

Around one in two mothers consumed alcohol during pregnancy, but only around one in ten consumed a large amount of alcohol in an episodic manner or at established hazardous levels. The mother's current alcohol consumption generally matched the drinking pattern during pregnancy, which was predominantly a low–moderate consumption (see Table 2).

Mother's alcohol consumption and child mental disorders

The presence of a mental disorder was observed in 45.6% (37/81) of children according to K-SADS-PL interviews (see Table 3). When we divided the children's diagnoses into disruptive disorders (externalizing) and emotional disorders

Table 2 Patterns of alcohol consumption of the 81 mothers surveyed

Alcohol variables	<i>N</i> (%)
Current potential alcohol problem (AUDIT)	14 (17.3)
Risk drinking during pregnancy (T-ACE)	15 (18.5)
Harmful use and dependence syndrome during pregnancy (CID)	7 (8.6)
Any alcohol use during pregnancy ^b	41 (53.9)
Binge drinking during pregnancy ^a	10 (12.8)
Alcohol consumption in all trimesters of pregnancy ^b	18 (23.7)
Number of trimesters of alcohol consumption during pregnancy ^b	0 trim—35 (46.1) 1 trim—11 (14.5) 2 trim—12 (15.8) 3 trim—18 (23.7)

Trim trimester

^aThree missing cases

^bFive missing cases

Table 3 Children's mental disorders according to K-SADS-PL (DSM-IV)

Psychiatric diagnoses	Male (<i>n</i> = 35) <i>N</i> (%)	Female (<i>n</i> = 46) <i>N</i> (%)
Depressive disorder	2 (5.7)	3 (6.5)
Panic disorder	1 (2.9)	0 (0)
Separation anxiety disorder	1 (2.9)	2 (4.3)
Simple phobia	4 (11.4)	1 (2.2)
Social phobia	3 (8.6)	8 (17.4)
Generalized anxiety disorder	1 (2.9)	2 (4.3)
Obsessive compulsive disorder	1 (2.9)	0 (0)
Enuresis	4 (11.4)	2 (4.3)
Encopresis	1 (2.9)	2 (4.3)
ADHD	13 (37.1)	8 (17.4)
Oppositional defiant disorder	9 (25.7)	5 (10.9)
Transient tic disorders	0 (0)	1 (2.2)
Mental retardation	0 (0)	2 (4.3)

(internalizing), we found 22.2% (18/81) with externalizing disorders and 32.1% (26/81) with internalizing ones.

Our research did not find correlations between children's internalizing disorders and any variable that investigated their mothers' mental health and alcohol consumption. On the other hand, externalizing disorders were associated with binge drinking at any time during pregnancy ($\chi^2 = 4.60$, $df = 1$, $p = 0.03$), number of trimesters of alcohol consumption ($\chi^2 = 7.75$, $df = 3$, $p = 0.05$), and alcohol consumption in all trimesters ($\chi^2 = 6.27$, $df = 1$, $p = 0.01$). The effects of binge drinking, number of trimesters, and all trimesters of alcohol consumption on the variance of externalizing

disorders were 5.8% (Cramer's $V = 0.24$), 10% (Cramer's $V = 0.32$), and 8.4% (Cramer's $V = 0.29$), respectively.

ADHD

Within the externalizing disorders, 81% (21/26) of children were suffering from ADHD, which drew our attention to ADHD as a main outcome. Compared to children without ADHD, children with ADHD had a significant greater proportion of mothers who had consumed alcohol in a binge manner, in more trimesters of pregnancy, and in all trimesters of pregnancy (Table 4). Mothers with binge drinking, with more trimesters of alcohol consumption, and with alcohol consumption in all trimesters during pregnancy explained 5.3% (Cramer's $V = 0.23$), 11.6% (Cramer's $V = 0.34$), and 9% (Cramer's $V = 0.30$) of the variance of ADHD's occurrence, respectively.

Prior to ascertaining a model of logistic regression, we investigated confounding risk factors for ADHD and FASD. In this initial comparison between mothers of children with ADHD and those without ADHD, our study did not find any significant difference in the mean age ($t = -1.86$, $df = 79$, $p = 0.07$), racial diversity ($\chi^2 = 3.35$, $df = 2$, $p = 0.19$), schooling (LR = 1.13, $df = 3$, $p = 0.77$), attendance at a religious institution ($\chi^2 = 0.55$, $df = 1$, $p = 0.46$), first pregnancy ($\chi^2 = 1.15$, $df = 1$, $p = 0.29$), number of children ($t = -0.58$, $df = 79$, $p = 0.56$), family income (LR = 3.32, $df = 3$, $p = 0.34$), family/environmental stressors ($\chi^2 = 3.30$, $df = 1$, $p = 0.07$), and tobacco use during pregnancy ($\chi^2 = 2.61$, $df = 1$, $p = 0.11$). Therefore, these confounding risk factors were not included in our logistic regression. The independent variable, number of trimesters of alcohol consumption

Table 4 Association between maternal variables and ADHD in the offspring

Maternal variables	Children with ADHD (<i>n</i> = 21)	Children without ADHD (<i>n</i> = 60)	χ^2 (<i>df</i>)	<i>p</i>
Current mental disorder (SRQ)	13	19	5.95 (1)	0.01
Current outpatient psychiatric treatment	5	5	3.44(1)	0.06
Current potential alcohol problem (AUDIT)	5	9	0.84 (1)	0.36
Risk drinking during pregnancy (T-ACE)	6	9	1.90 (1)	0.17
Harmful use and dependence syndrome during pregnancy (CID)	3	4	1.14 (1)	0.28
Alcohol use during pregnancy	11 ^a	30 ^c	0.01 (1)	0.91
Binge drinking during pregnancy	5 ^b	5 ^a	4.09 (1)	0.04
Alcohol consumption in all trimesters of pregnancy	9 ^a	9 ^c	6.82 (1)	0.01
Number of trimesters of alcohol consumption during pregnancy	0 trim = 9 1 trim = 1 2 trim = 1 3 trim = 9 ^a	0 trim = 26 1 trim = 10 2 trim = 11 3 trim = 9 ^c	8.90 (3)	0.03

Trim trimester

^aOne missing case

^bTwo missing cases

^cFour missing cases

during pregnancy, was not included in the logistic regression due to its statistical singularity with alcohol consumption in all trimesters.

On the other hand, children with ADHD presented a significant greater proportion of mothers who had mental disorders (see Table 4), and, as expected, there were a greater proportion of males (13/35) than females (8/46) ($\chi^2 = 4.03$, $p = 0.04$).

We tested a model of hierarchical logistic regression to assess the influence of alcohol consumption in all trimesters of pregnancy and binge drinking at any time during pregnancy on the occurrence of ADHD at 12 years of age, controlling for the effects of gender and current maternal mental disorders.

The Omnibus Test of alcohol use variables supported our model as being worthwhile ($\chi^2 = 12.56$, $df = 2$, $p = 0.002$). When both alcohol use variables were added to the covariates model, the amount of variation in the occurrence of ADHD increased from 16 to 35% (Nagelkerke R squared) and the percentage of children predicted accurately to have ADHD (positive predictive value) increased from 60 to 100%.

Both the effects of regular use of alcohol and binge drinking were major factors associated with the risk of ADHD. When compared to children whose mother did not drink, children whose mothers consumed alcohol in a binge manner at any time of pregnancy or in all trimesters of pregnancy were around five times as likely to suffer from ADHD, after controlling for the potential confounding effects of covariates (Table 5). Nevertheless, the covariates also revealed main effects, showing that the odds of ADHD are four times higher for male children or when children had a mother suffering from a mental disorder.

Discussion

Our study showed an association between the prenatal alcohol exposure and the presence of mental disorders in the child at 12 years of age. Children with externalizing disorders were linked to mothers who used alcohol during pregnancy. More specifically, children with ADHD were more likely to have mothers who consumed low–moderate

alcohol doses in all trimesters and/ or in a binge manner during pregnancy.

ADHD prevalence rates in children exposed to alcohol prenatally are higher than those in the general population. Children in the general population have an estimated pooled prevalence of 7.2% [27], whereas children with FAS have a pooled prevalence of 51.2% [11]. The difference of ADHD prevalence among children exposed to alcohol during pregnancy may be related to the maternal pattern of alcohol consumption. Our study found a prevalence rate of 37% with light–moderate drinkers whereas another study [28], which also used clinical interviews and investigated children at around 12 years of age, found a rate of 95% with heavy drinkers.

Even with most mothers consuming alcohol in a low–moderate range, our results highlighted the independent harmful role of alcohol when consumed during all trimesters of pregnancy. Previous large population-based cohort studies [29, 30] did not show any negative effects of low–moderate alcohol use, however, a recent meta-analysis [31] did show a trend, albeit inconclusive, for the association between low dose alcohol use and behaviour problems assessed by self-questionnaires. When the assessment of alcohol use was restricted to one or two trimesters, studies have not found associations between low–moderate doses and inattention/hyperactivity symptoms [32]. On the other hand, when clinical interviews and prospective design [33, 34] are used, the effects of the low–moderate use of alcohol emerge as a risk factor for externalizing behaviours and inattention/hyperactivity in the offspring. Our findings may suggest that the risk for ADHD with low–moderate prenatal alcohol exposure can be mediated by the regular consumption of alcohol, that is, by alcohol consumption during all trimesters of pregnancy.

In addition to the regular use of alcohol, our study also supported the independent association between binge drinking and ADHD. The presence of ADHD increased five times in children whose mothers consumed four or more drinks at any occasion during pregnancy. Combining binge drinking and alcohol use in all trimesters of pregnancy led to an enlargement of 19% on the variance of ADHD occurrence, regardless of the mediator and moderator variables that also influenced the occurrence of ADHD.

Our results found gender influence and mother's mental health as moderator and mediator risk factors, which

Table 5 Children's gender, mother's mental disorder, and alcohol consumption pattern during pregnancy as risk factors for ADHD in 12-year-old offspring

Variable	<i>B</i>	SE	Wald χ^2	<i>p</i>	Odds ratio	95% CI
Gender	1.36	0.63	4.65	0.03	3.89	1.13–13.35
Current mental disorder (SRQ)	1.48	0.62	5.63	0.02	4.37	1.29–14.80
Alcohol consumption in all trimesters of pregnancy	1.63	0.65	6.25	0.01	5.11	1.42–18.38
Binge drinking during pregnancy	1.55	0.77	4.04	0.04	4.72	1.04–21.47

increased the risk of ADHD by four times in the offspring. Children's mental disorders can be influenced by genetic loading as well as dysfunctional behaviour towards the child [34]. Boys are three times more likely than girls to suffer from ADHD [35], and have a higher prevalence of FASD than girls in the 10–19 age range (34.1 vs 21.7 per 1000) [36]. Furthermore, mothers suffering from mental disorders are less empathic and emotionally available [34, 37].

This association between ADHD and environmental and genetic factors [38, 39], generates methodological constraints in the identification of specific risk factors [40]. We controlled for many potential confounding factors, but overlapping and interactional effects cannot be removed completely. Randomized controlled studies are necessary to confirm our observed associations since we cannot exclude the influence of other unmeasured confounding variables. For example, although we investigated the mental health of the mothers, we did not specifically survey the occurrence of ADHD in both parents, which could have given a better indication of the genetic load. Moreover, the inherent missing cases in our long-term follow-up may be stressed by sample bias; many mothers may have accepted to participate in the research because they were concerned about their children or their own mental health.

As we have seen, the mothers of our survey regularly attended prenatal care and had low–moderate alcohol consumption. In contrast, late prenatal care is associated with heavy use of alcohol, which in turn is associated with high prevalence of FAS. In clinical samples like ours, the prevalence of FAS is very low [41] because the low–moderate alcohol consumption predominates. Furthermore, in our study, other risk cofactors associated with FAS, such as older women (≥ 28 years) at the birth of the child and previous pregnancies [42], may have been attenuated by the significant proportion of young women in their first pregnancy (35,8%).

Conclusion

Our study provides evidence that prenatal alcohol exposure is associated with ADHD in childhood. After controlling for many confounding variables and assessing the effects of mediator and moderator risk factors, an episodic and a regular pattern of alcohol consumption demonstrated independent effects. Binge drinking at any time during pregnancy or alcohol consumption in all trimesters of pregnancy, even at low–moderate doses, was associated with a fivefold increased odds of ADHD in the offspring at 12 years of age.

This implicates that interventions with pregnant women to reduce binge drinking and the regular use of low–moderate alcohol doses may lead to a significant decrease in their children developing ADHD.

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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