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SHORT COMMUNICATION

Moderate alcohol drinking and risk of preterm birth

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Objective: We have analysed the association between alcohol drinking before and during the three trimesters of pregnancy and risk of preterm birth of babies with normal weight for gestational age or with low weight for gestational age (SGA).
Design: Case–control study.
Setting: General and university hospitals in Italy.
Subjects: Cases were 502 women who delivered preterm births <37 weeks gestation. The controls included 1966 women who gave birth at term (≥ 37 weeks of gestation) to healthy infants of normal weight (ie between 10th and 90th centile according to the Italian standard) on randomly selected days at the hospitals where cases had been identified.
Interventions: Interview.
Results: No increased risk of preterm birth was observed in women drinking one or two drinks/die in pregnancy, but three or more drinks/die increased the risk (multivariate odds ratios (OR) 2.0 for ≥ 3 drinks during the first trimester, 1.8 during the second and 1.9 during the third). When the analysis was conducted separately for preterm births with normal weight or SGA, the increased risk was observed in preterm SGA only (multivariate OR for ≥ 3 drinks/die during the first trimester $= 3.6$, 95% confidence interval (CI) 1.3–11.1); the estimated multivariate OR for ≥ 3 drinks/die during the first trimester of preterm babies with normal weight for gestational age was only slightly above unity and not statistically significant (multivariate OR 1.4, 95% CI 0.5–3.7).
Conclusions: The study shows an increased risk in mothers who drink ≥ 3 die units alcohol in pregnancy of preterm births.
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Introduction

The potential negative effect of alcohol drinking in pregnancy on birth weight and preterm delivery is controversial (Die *et al,* 1989; Shu *et al,* 1995; Windham *et al,* 1995; Passaro *et al,* 1996; Makarechian *et al,* 1998). For example, a recent cohort study based on postal questionnaires conducted in Denmark (Kesmodel *et al,* 2000) has suggested that heavy alcohol drinking during the first 30 weeks of gestation increases the risk of preterm births about three-fold. In biological terms the association has been explained in terms of an enhanced prostaglandin level in alcohol drinkers, and prostaglandins can cause preterm birth (Cook & Randal 1998). Other reports showed an increased risk of preterm birth also for moderate alcohol drinking. For example, a moderate increased risk of delivery of preterm babies with low weight for gestational age at birth was found to be associated with alcohol drinking in a Canadian study (McDonald *et al,* 1992). A prospective investigation based on 2714 single live births conducted in the US during 1988–1992 indicated an increased risk of preterm birth, but not of small weight for gestational age (SGA) (Lundsberg *et al,* 1997).

Further, the potentially different role of alcohol drinking before pregnancy or at different trimesters of pregnancy is unclear. For example, an increased risk of preterm birth has been found to be associated with increasing alcohol consumption before pregnancy in one study (Little *et al,* 1986). Moderate intake increases the risk of preterm birth for alcohol drinking late in pregnancy, but not early in pregnancy in another study (Lundsberg *et al,* 1997).

In this paper we have analysed the association between alcohol drinking before and during the three trimesters of pregnancy using data from a case–control study conducted in Italy. This study provides the opportunity of analysing the

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effect of alcohol intake on the risk of preterm birth of babies with normal or low weight for gestational age and the potential interaction between alcohol drinking and risk factors for preterm birth.

Methods

We conducted a case–control study on risk factors for preterm births. The cases were 502 women who delivered preterm births 28 to <37 weeks gestation (mean age 31 y, range 16–48) identified at the Clinica Luigi Mangiagalli (the largest obstetric hospital in Milan) and the Obstetric and Gynecology Clinic of the University of Verona.

An infant was defined as SGA if the weight was less than the 10th centile on comparison of the birth weight of each single baby with that expected for the same gestational age and sex, according to Italian standards (Parazzini *et al*, 1995).

Table 1 Distribution of study subjects according to selected factors[a]

	Preterm births		Controls	*OR (95% CI)*	
	SGA	*NGA*		*SGA*	*NGA*
	No. (%)	*No. (%)*	*No. (%)*	*No. (%)*	*No. (%)*
Age (y)					
<25	15 (10.5)	36 (10.0)	180 (9.2)	1+	
25–29	44 (30.8)	118 (32.9)	637 (32.4)	0.9 (0.5–1.8)	1.0 (0.7–1.6)
30–34	55 (38.5)	117 (32.6)	767 (39.0)	0.9 (0.5–1.7)	0.9 (0.6–1.3)
≥35	29 (20.3)	88 (24.5)	382 (19.4)	1.1 (0.5–2.4)	1.4 (0.9–2.2)
Gestational week at birth mean (range)	34 (28–36)	33 (23–36)	39 (37–42)	—	—
Education (y)					
≤6	10 (7.0)	17 (4.7)	53 (2.7)	1+	1+
7–13	105 (73.4)	274 (76.3)	1439 (73.2)	0.4 (0.2–1.0)	0.7 (0.4–1.2)
≥14	28 (19.6)	68 (18.9)	473 (24.1)	0.4 (0.2–1.1)	0.6 (0.3–1.0)
Marital status					
Married	138 (96.5)	350 (97.5)	1934 (98.4)	1+	1+
Unmarried	5 (3.5)	9 (2.5)	32 (1.6)	1.2 (0.4–3.8)	1.5 (0.7–3.3)
Parity					
0	103 (72.0)	220 (61.3)	1103 (56.1)	1+	1+
1	31 (21.7)	100 (27.9)	693 (35.3)	0.5 (0.3–0.8)	0.7 (0.6–1.0)
≥2	9 (6.3)	39 (10.9)	170 (8.7)	0.5 (0.2–1.0)	1.0 (0.6–1.5)
Smoking during the first trimester of pregnancy					
No	103 (72.0)	281 (78.3)	1677 (85.3)	1+	1+
Yes	40 (28.0)	78 (21.7)	289 (14.7)	2.6 (1.7–4.0)	1.6 (1.2–2.0)
Coffee consumption during pregnancy					
No	34 (23.8)	84 (23.4)	441 (22.4)	1+	1+
Yes	109 (76.2)	275 (76.6)	1525 (77.6)	1.0 (0.7–1.6)	0.9 (0.7–1.2)
Previous preterm births[b]					
No	27 (67.5)	105 (75.5)	815 (94.4)	1+	1+
Yes	13 (32.5)	34 (24.5)	48 (5.6)	8.7 (3.9–19.7)	5.3 (3.2–8.8)
Maternal BMI at contraception					
≤20	67 (47.2)	139 (39.6)	776 (39.6)	1+	1+
21–25	55 (38.7)	168 (47.9)	982 (50.1)	0.6 (0.4–0.9)	0.9 (0.7–1.1)
>25	20 (14.1)	44 (12.5)	201 (10.3)	0.6 (0.3–1.2)	0.9 (0.6–1.3)
Hypertension in pregnancy					
No	74 (51.8)	273 (76.0)	1863 (94.8)	1+	1+
Yes	69 (48.2)	86 (24.0)	103 (5.2)	17.4 (11.6–26.1)	5.8 (4.2–8.0)

[a]In some cases, the sum does not add up to the total due to missing values: +, reference category; OR=odds ratios adjusted for age, centre, education, parity and smoking during the first trimester of pregnancy, gestational hypertension, history of preterm births. BMI= body mass index (kg m^{-2}).
[b]Parous women only. SGA= small for gestational age. NGA= normal for gestational age.

The controls were women who gave birth at term (≥37 weeks of gestation) to healthy infants of normal weight (ie between the 10th and 90th centile according to Italian standards) (Parazzini *et al,* 1995) on randomly selected days at the hospitals where cases had been identified. The interviewers surveyed the obstetric wards on days established at random to interview controls whose age was comparable with cases. A total of 1966 controls (mean age 31 y, range 14–43) were interviewed by six interviewers. The overall participation was over 95% for cases and controls.

Information was obtained on general sociodemographic habits, personal characteristics and habits, gynaecological and obstetric history, smoking and coffee consumption in pregnancy. Questions on alcohol included the number of days per week each type of alcoholic beverage (red and white wine, beer and spirits) was consumed before pregnancy and in each trimester of pregnancy and the average number of drinks per die and the duration of the habit in years. From these data, an estimate of the total daily average alcohol intake was derived, assuming a comparable pure alcohol content in each type of drink (125 ml red wine = 333 ml beer = 30 ml spirits = ~12 g pure alcohol). Red wine alone accounted for ~90% of the alcohol consumed by women in this population. Specific attention was paid to obtaining, from cases and controls, information on alcohol consumption at conception and during various trimesters of pregnancy. All information, birth weight and week of gestation at birth apart, were obtained from personal interviews. The presence of hypertension in pregnancy was checked with clinical records.

We computed the odds ratios (OR) adjusted for age, as estimators of the relative risks, of preterm births with their 95% approximate confidence intervals (CI) using the Mantel–Haenzel procedure.

Further, to account simultaneously for the effects of several potential confounding factors, we used unconditional multiple logistic regression, with maximum likelihood fitting, to obtain OR and their corresponding 95% CI (Breslow & Die, 1980).

Included in the regression equations were terms for age, centre, education and terms found significantly associated in this data set with the risk of preterm birth. These factors are

Table 2 Odds ratios of preterm birth according to alcohol drinking[a]

	Preterm births		*Controls*	*OR*		
	SGA No. (%)	*NGA No. (%)*	*No. (%)*	*Total preterm births*	*NGA*	*SGA*
Alcohol drinking before conception (units/die)						
0	79 (55.2)	202 (56.3)	1132 (57.6)	1+	1+	1+
<1	17 (11.9)	41 (11.4)	245 (12.5)	1.0 (0.7–1.4)	0.9 (0.6–1.4)	1.2 (0.6–2.1)
1	28 (19.6)	64 (17.8)	333 (16.9)	1.2 (0.9–1.6)	1.1 (0.8–1.5)	1.4 (0.9–2.3)
2	15 (10.5)	38 (10.6)	207 (10.5)	0.9 (0.6–1.3)	0.9 (0.6–1.4)	1.0 (0.5–1.8)
≥3[b]	4 (2.8)	14 (3.9)	49 (2.5)	1.5 (0.8–2.6)	1.6 (0.8–3.0)	1.0 (0.3–3.3)
First trimester						
0	98 (68.5)	245 (68.3)	1345 (68.4)	1+	1+	1+
<1	17 (12.0)	39 (10.9)	187 (9.5)	1.3 (0.9–1.8)	1.2 (0.8–1.8)	1.5 (0.8–2.7)
1	14 (9.8)	42 (11.7)	281 (14.3)	0.8 (0.5–1.1)	0.8 (0.5–1.2)	0.7 (0.4–1.3)
2	7 (4.9)	27 (7.5)	131 (6.7)	0.9 (0.6–1.5)	1.0 (0.7–1.6)	0.7 (0.3–1.8)
≥3[b]	7 (4.9)	6 (1.7)	22 (1.1)	2.0 (1.0–4.5)	1.4 (0.5–3.7)	3.6 (1.3–11.1)
Second trimester						
0	99 (69.2)	247 (68.8)	1353 (68.8)	1+	1+	1+
<1	16 (11.2)	38 (10.6)	190 (9.7)	1.2 (0.9–1.7)	1.1 (0.8–1.7)	1.4 (0.8–2.6)
1	15 (10.5)	43 (12.0)	273 (13.9)	0.8 (0.6–1.1)	0.9 (0.6–1.7)	0.7 (0.4–1.3)
2	8 (5.6)	25 (7.0)	127 (6.5)	0.9 (0.6–1.5)	0.9 (0.6–1.5)	0.8 (1.9)
≥3[c]	5 (3.5)	6 (1.7)	23 (1.2)	1.8 (0.8–4.1)	1.5 (0.6–3.8)	2.9 (0.9–9.6)
Third trimester						
0	101 (70.6)	247 (68.8)	1353 (68.8)	1+	1+	1+
<1	14 (9.8)	38 (10.6)	190 (9.7)	1.1 (0.8–1.5)	1.0 (0.7–1.5)	1.2 (0.6–2.2)
1	16 (11.2)	43 (12.0)	272 (13.8)	0.8 (0.6–1.2)	0.8 (0.6–1.2)	0.7 (0.4–1.3)
2	7 (4.9)	25 (7.0)	129 (6.6)	0.9 (0.6–1.4)	0.9 (0.6–1.5)	0.7 (0.3–1.7)
>3[c]	5 (3.5)	6 (1.7)	22 (1.1)	1.9 (0.9–4.3)	1.6 (0.6–4.0)	3.1 (0.9–10.2)

[a]In some cases, the sum does not add up to the total due to missing values. +reference category. OR, odds ratios adjusted for age, centre, education, parity, coffee consumption during pregnancy and smoking during the first trimester of pregnancy, gestational hypertension and history of preterm births. BMI= body mass index ($kg\,m^{-2}$)

SGA=small for gestational age; NGA=normal for gestational age.

[b]Including subjects drinking 10 units/die or more: one case of NCA and four controls, no cases of SGA.

[c]Including subjects drinking 10 units/die or more: one case of NGA and two controls, no cases of SGA.

Table 3 Odds ratios of preterm birth according to alcohol drinking during the first trimester of pregnancy and selected covariates

	1		2		≥3	
	SGA	*NGA*	*SGA*	*NGA*	*SGA*	*NGA*
Maternal age (y)						
<25	0.5	1.0	NS	1.5	NS	2.6
25–29	1.1	1.0	0.5	0.7	1.2	0.9
30–34	1.0	0.7	1.1	1.4	2.4	2.2
≥35	0.2	0.8	0.3	0.8	11.1	1.4
Previous preterm births						
No	0.4	0.9	0.8	0.7	3.0	1.7
Yes	0.3	1.3	Ne	6.0	ne	ne
Smoking during first trimester						
No	0.8	0.7	0.6	0.9	1.6	1.5
Yes	0.6	1.4	1.3	1.4	6.1	1.1
Gestational hypertension						
No	0.6	0.9	1.1	0.9	3.4	1.5
Yes	1.0	0.7	0.6	1.5	2.2	1.3

Reference category: no alcohol drinking/<1 unit/die;
+, adjusted for age; SGA=small for gestational age; NGA=normal for gestational age; ne=not estimated.

listed in the footnotes of tables. Only multivariate estimates are presented in the text and in the tables if not otherwise specified.

Results

Table 1 shows the distribution of cases and controls according to age, gestational weeks at births and selected factors. Smoking during pregnancy gestational hypertension and a history of preterm births increased the risk of preterm birth. No significant association emerged between education, marital status, parity, coffee consumption and maternal body mass index at conception and risk of preterm birth. Alcohol intake and risk of preterm birth is considered in Table 2. No association emerged between alcohol intake before conception and risk of preterm birth.

No increased risk of preterm birth was observed in women drinking one or two drinks/die in pregnancy, but three or more drinks/die increased the risk (multivariate OR 2.0 (95% CI 1.0–4.5) for ≥3 drinks during the first trimester, 1.8 (95% CI 0.8–4.0) during the second and 1.9 (95% CI 0.9–4.3) during the third). These findings were largely consistent when the analysis was performed separately for data collected in the two hospitals: for example, the multivariate ORs of preterm birth delivered in drinkers during the first trimester of ≥3 drinks/die were 1.8 for subjects collected in Verona and 2.0 for those collected in Milan. Likewise, the inclusion or exclusion in the analysis of terms for the interviewer did not change the estimated OR (data not shown).

When the analysis was conducted separately for preterm births associated or not with SGA, the increased risk was observed only for preterm SGA (multivariate OR for ≥3 drinks/die 3.6, 95% CI 1.3–11.1). The estimated multivariate OR for >3 drinks/die of preterm birth of babies with normal weight for gestational age was only slightly above unity and not statistically significant (multivariate OR 1.4, 95% CI 0.5–3.7).

Table 3 considers the effect of alcohol drinking on the risk of preterm birth during the first trimester of pregnancy in strata of maternal age, smoking habits, hypertension and history of preterm birth: no interaction emerged.

Comment

A specific interest of this analysis is the opportunity of analysing the effect of alcohol intake on the risk of preterm birth associated or not with SGA. The increased risk of preterm birth associated in alcohol drinkers was present only for an intake of three ≥3 drinks/die. Further there is a tendency towards a greater risk among SGA babies compared with NGA, but the differences are not significant. The effect of alcohol was not affected by smoking—thus not supporting an interaction effect (Larroque *et al,* 1993)—and was similar in strata of maternal age, and in women with and without gestational hypertension and history of preterm birth.

Potential limitations of this study should be considered. First of all, information on alcohol drinking was retro-

spectively collected after delivery. The assessment of alcohol consumption was based on self-reporting, so some underestimates could have occurred. However, in Italy, alcohol consumption is socially accepted and recommendations to avoid alcohol in pregnancy have not received widespread attention and are not routinely advocated by gynaecologists. A good reporting of alcohol intake at postpartum interview in women delivering normal or low birth weight infants has also been recently documented (Delgado-Rodriguez *et al,* 1995). Other sources of bias, including selection or confounding factors, are also unlikely to have produced marked effects, especially considering that cases and controls were interviewed in the same institution and that participation was practically complete. Further, the findings were largely consistent when the analysis was performed separately for cases and controls collected in the two hospitals or by different interviewers or when terms for centre and interviewers were included in the models. We did not analyse information on nutritional status, but inclusion in the model of BMI did not change the estimated OR (data not shown). Further, the questionnaire was satisfactorly reproducible (D'Avanzo *et al,* 1997). Another potential limitation is study power. For example, with our data, considering a prevalence of drinkers of about 45% in the first trimester of pregnancy, we can identify an OR of preterm births for drinkers of about 2.0.

A specific interest of the study lies in the fact that it analyses the association between alcohol drinking and preterm birth and SGA in a Southern European population, characterized by a widepread use of a lower dose of alcohol drinking in alcohol with North America or European populations, characterized by a lower prevalence of drinkers, but by a higher frequency of heavy drinkers.

The results of this study confirm findings of a recent cohort study that showed a three times increased risk of preterm birth in women drinking 10 or more alcohol services per week during the 30 weeks of gestation (Kesmodel *et al,* 2000). Similar results also emerged from other studies, although no association between alcohol drinking and risk of preterm birth was, for example, found in a study conducted in California (Windham *et al,* 1995) and in the Preterm Prediction Study (Andrews *et al,* 2000).

There are consistent findings on the association between low birth weight and alcohol intake: studies on the issue have shown a direct association (Windham *et al,* 1995; McDonald *et al,* 1992). Our results give support to this finding. In fact, in our study association of alcohol intake with the risk of preterm was observed only in women who delivered babies with low birth weight for gestational age. The biological mechanism through which alcohol drinking affects foetal growth is not completely understood. Alcohol or its metabolites have been hypothesized to affect foetal development causing foetal hypoxia, impairing cell proliferation, or affecting placental development (Abel, 1982).

In conclusion, the study shows an increased risk in mothers who drink 3 units/die of alcohol in pregnancy of preterm birth This effect is not due to potential confoundings such as smoking

References

Abel EL (1982): Consumption of alcohol during pregnancy: a review of effects on growth and development of offspring. *Hum. Biol.* **54**, 421–453.

Andrews WW, Goldenberg RL, Mercer B, Iams J, Meis P, Moawad A, Das A, Vandorsten JP, Caritis SN, Thurnau G, Miodovnik M, Roberts J & McNellis D (2000): The preterm prediction study: association of second-trimester genitourinary chlamydia infection with subsequent spontaneous preterm birth. *Am. J. Obstet. Gynecol.* **183**, 662–668.

Breslow NE & Die NE (1980): *Statistical Methods in Cancer Research. The Analysis of Case Control Studies*. Vol. **I**, IARC Publication No. 32, Lyon, France: IARC.

Cook JL & Randal CL (1998): Ethanol and parturition: a role for prostaglandins. *Prostaglandins Leukort. Essent. Fatty Acid* **58**, 135–142.

Die NL, Jasperse D, Richardson G, Robles N, Sambamoorthi U, Taylor P, Scher M, Stoffer D & Cornelius M (1989): Prenatal exposure to alcohol: effect on infant growth and morphologic characteristics. *Pediatrics* **84**, 536–541.

Delgado-Rodriguez M, Gomez-Olmedo M, Bueno-Cavanillas A, Garcia-Martin M & Galvez-Vargas R (1995): Recall bias in a case control study of low birth weight. *J. Clin. Epidemiol.* **48**, 1133–1140.

D'Avanzo B, La Vecchia C, Katsouyanni K, Negri E & Trichopoulos D (1997): An assessment, and reproducibility of food frequency data provided by hospital controls. *Eur. J. Cancer Prev.* **6**, 288–293.

Kesmodel U, Olsen SF & Secher NJ (2000): Does alcohol increase the risk of preterm delivery? *Epidemiology* **11,** 512–518.

Larroque B, Kaminski M, Lelong N, Subtil D & Dehaene P (1993): Effects on birth weight of alcohol and caffeine consumption during pregnancy. *Am. J. Epidemiol* **137**, 941–950.

Little RE, Asker RL, Sampson PD & Renwick JH (1986): Fetal growth and moderate drinking in early pregnancy. *Am. J. Epidemiol.* **123**, 270–278.

Lundsberg LS, Bracken MB & Saftlas AF (1997): Low-to-moderate gestational alcohol use and intrauterine growth retardation, low birthweight, and preterm delivery. *Ann. Epidemiol.* **7**, 498–508.

Makarechian N, Agro K, Devlin J, Trepanier E, Koren G & Einarson TR (1998): Association between moderate alcohol consumption during pregnancy and spontaneous abortion, stillbirth and premature birth: a meta-analysis. *Can. J. Clin. Pharmacol.* **5**, 169–176.

McDonald AD, Armstrong BG & Sloan M (1992): Cigarette, alcohol, and coffee consumption and prematurity. *Am. J. Public Health* **82**, 87–90.

Parazzini F, Cortinovis I, Bortolus R, Fedele L & Decarli A (1995): Weight at birth by gestational age in Italy. *Hum. Reprod.* **10**, 1862–1963.

Passaro KT, Little RE, Savitz DA, Noss J & the ALSPAC Study Team (1996): The effect of maternal drinking before conception and in early pregnancy on infant birthweight. *Epidemiology* **7**, 377–383.

Shu XO, Hatch MC, Mills J, Clemens J & Susser M (1995): Maternal smoking, alcohol drinking, caffeine consumpion, and fetal growth: results from a prospective study. *Epidemiology* **6**, 115–120.

Windham GC, Fenster L, Hopkins B & Swan SH (1995): The association of moderate maternal and paternal alcohol consumption with birthweight and gestational age. *Epidemiology* **6**, 591–597.