

## REVIEW

### WOMEN, ALCOHOL AND THE MENSTRUAL CYCLE

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**Abstract** — This review presents evidence which implicates a role for menstrual cycle phase in the response of pre-menopausal women to moderate alcohol intake. It is concluded that the majority of published studies have suffered from poor methodological design and have employed inadequate means of cycle phase identification. Contradictory and ill-founded findings have been reported. The best evidence to date suggests that women eliminate alcohol more rapidly during the mid-luteal phase of the cycle. This finding needs to be substantiated by further studies.

#### INTRODUCTION

Relatively few studies have investigated a possible link between alcohol and the menstrual cycle but, paradoxically, it is relatively common to exclude women from alcohol-related investigations, because of assumed cycle-related interactions. This deficiency in our knowledge ought to be addressed. Two possible physical effects of moderate alcohol intake in pre-menopausal women merit investigation. Firstly, the absorption, metabolism and elimination of alcohol may be affected by the hormonal pattern which characterizes the monthly menstrual cycle. Secondly, the reverse may be true; alcohol, acting directly or indirectly, could alter the levels of the female hormones and, as a consequence, disrupt the normal menstrual cycle pattern. The following account reviews research addressed toward the first possibility — does the pharmacokinetic response to ethanol vary across the stages of the menstrual cycle?

#### PHARMACOKINETIC RESEARCH EVIDENCE

Research studies and their main findings are summarized in Table 1. One of the first research groups to report their findings (Jones and Jones,

1976) suggested that during the pre-menstrual phase (21–28 days) of the cycle (days assumed to be characterized by high levels of the hormones oestrogens and progesterone) women attained significantly higher blood alcohol levels (BALs) and faster alcohol absorption rates than women tested at the flow period (days 1–3) and the inter-menstrual period (days 13–18). Conversely, Zeiner and Kegg (1980) concluded that days of elevated sex steroids (around day 24 of the cycle) correlated with a reduced peak BAL and slow alcohol clearance rates. However, Marshall *et al.* (1983), Hay *et al.* (1984), Brick *et al.* (1986), Linnoila *et al.* (1980) and Cole-Harding and Wilson (1987) could find no evidence that peak BAL or elimination rate varied with cycle phase. The study of Freitag and Adesso (1993) examined heavy drinkers but reached similar conclusions. Sutker *et al.* (1987) also found that peak BAL did not vary across the cycle, but reported that alcohol was eliminated in significantly less time during the mid-luteal phase of the cycle.

The apparent disparity between the various research findings may be explained in part by poor methodological design. Thus, if the proposal that alcohol pharmacokinetics will be affected by the changing hormone levels of the menstrual cycle is to be tested, it is imperative that adequate checks

Table 1. Studies investigating the pharmacokinetic response of pre-menopausal women to acute alcohol intake

Study	No. of subjects (age in years)	Phases tested and designation	Cycle phase designation method	Alcohol dose and administration	Drink time	Mean peak BAL (time interval of BAL measurement)	Main conclusions
Jones and Jones (1976)	20 (college students)	(1) Menstrual flow, days 1-3 (2) Inter-menstrual, days 13-18 (3) Pre-menstrual, days 21-28 Each subject tested at two of three cycle phases	Calendar	0.53 g/kg ethanol/kg body weight diluted 1:4 with orange juice Light breakfast, then fasted until testing began 4 h later	5 min	72 mg% (5-10 min)	Subjects tested during the pre-menstrual period displayed significantly higher peak BALs than women in the menstrual or inter-menstrual period
Zeiner and Kegg (1980)	10	(1) First day of menstrual flow, day 1 (2) Day 24 Each subject tested on each day	Calendar	0.52 g/kg body weight ethanol mixed 1:4 with orange juice Light breakfast, then tested 3 h later	5 min	(10 min)	Peak BAL was higher and alcohol elimination rates were faster on day 1 than on day 24
Marshall <i>et al.</i> (1983)	9 (30)	(1) Mid-follicular days 8-10 (2) Mid-luteal days 22-24 Each subject tested at both phases	Elevated serum progesterone levels during the second half of cycle taken as indication of ovulation	0.5 g/kg body weight ethanol mixed 1:3 with orange juice Light breakfast, then tested 3 h later	1 min	88 ± 3 mg% (15 min)	Ethanol pharmacokinetics were similar in females throughout the menstrual cycle
Hay <i>et al.</i> (1984)	9 (20)	(1) Menstrual flow days 1-5 (2) Mid-cycle days 12-15 (3) Pre-menstrual days 26-28 Subjects tested at each of three phases	Calendar	Testing began after 8 h fast six drinks were administered per session at 40 min intervals three drinks contained 45 ml 40% v/v ethanol two drinks contained 30 ml 40% v/v ethanol, and one drink contained 15 ml 40% v/v ethanol to a total volume of 180 ml with tomato juice	6 min	77-130 mg% (40 min)	No differences in peak BAL as a function of menstrual cycle
Niaura <i>et al.</i> (1987)	13; 7 were contraceptive pill users (21)	(1) Menstrual flow (2) Mid-cycle (3) Pre-menstrual designation not given. Each subject tested at one phase	Calendar	0.65 g/kg body weight vodka mixed 1:4 with tonic water Testing began immediately after a standard breakfast	1/3 drink consumed every 20 min, drinking time 5 min	78 mg% (20 min)	No significant differences in BAL as a function of menstrual cycle were observed

Cole-Harding and Wilson (1987)	32 15	(1) Days 1-6 (2) Days 12-14 (3) Days 19-24 (4) No distinct phase Each subject tested at one phase	Calendar	0.8 g/kg body weight diluted 1:7 with soft drink Attempts made to maintain BAL close to 100 mg% for 3 h by a further alcohol administration. Overnight fast then standard breakfast. Alcohol administered 4 h later	1/10 of dose consumed every 1.5 min	100 mg% (10 min)	No significant differences in alcohol pharmacokinetics attributable to menstrual cycle phases reported
Sutker <i>et al.</i> (1987)	8 (21-31)	(1) Early follicular, days 2-7 (2) Ovulatory, around day 4 (3) Mid-luteal days 20-25 Each subject tested at each phase for two consecutive cycles	RIA of LH, FSH, progesterone and oestradiol	Two doses of alcohol studied 0.66 ml/kg and 1.0 ml/kg diluted 1:4 with decarbonated tonic water Testing began after a 10 h fast	15 min 20 min	80 mg% 115 mg% (5 min)	No differences in absorption time or peak BAL across phases of menstrual cycle. Mid-luteal phase of cycle was characterized by decreased elimination time, reduced area under the curve and faster disappearance rate when compared at early follicular and ovulatory phases
Brick <i>et al.</i> (1986)	10; six oral contraceptive users (21-24)	(1) Flow, days 1-3 (2) Mid-cycle, days 14-16 (3) Pre-menstrual, days 26-28. Each subject tested three times	Calendar	0.65 g/kg body weight diluted 1:3.5 with tonic 1 h after a light breakfast	1/3 of drink consumed every 20 min. Drinking time 5 min	83 mg% (20 min)	No effect of menstrual cycle phase on ethanol pharmacokinetics was observed
Linnoila <i>et al.</i> (1980)	10 (20-25)	9 days after onset of menses and 9 days after rise in body temperature	Body temperature rise in luteal phase	0.5, 0.8, 1.2 g/kg (mixed drink) Administered after 3 h fast	30 min	(30, 60 and 90 min)	No significant difference in BAL between two phases of menstrual cycle
Freitag and Adesso (1993)	48 (21.7)	Menstruation (days 1-4) Ovulation (days 13-18) Pre-menstruation (1-4 days before menstruation)	Calendar	1.1 ml of absolute alcohol per kg body weight (diluted 1:5 with tonic) Administered after 4 h fast	15 min	(15 min)	No significant difference in BAL across the cycle

BAL = blood alcohol level; USP = United States Pharmacopæia; RIA = radioimmunoassay; LH = luteinizing hormone; FSH = follicle stimulating hormone

are performed to ensure that ovulation has occurred. The menstrual cycle can be divided into two phases. The first, the follicular phase, leads up to mid-cycle when the egg is released. The second half of the cycle is the luteal phase. Each half of the cycle is ~ 14 days long. If an egg is not released (i.e. the cycle is anovulatory), the hormone secreting structure within the ovary, the corpus luteum, does not form at mid-cycle and the high levels of oestrogen and progesterone characteristic of the luteal phase are not produced. Thus the hormone profile of the second half of an ovulatory cycle is quite different from that of an anovulatory cycle. Very few studies have employed reliable methods to identify cycle phase and to distinguish between the two types of cycle. The errors associated with the calendar method and the thermal method are all well documented. Yet, despite this knowledge, some investigators have assumed that the hormone profile of the entire cycle can be predicted from a knowledge of the subject's report of menstrual period. The possibility that ovulation will not have occurred has been largely ignored. The work of Metcalf and Mackenzie (1980) provides cautionary evidence. They found that within the age group 20–24 years, only 62% of women ovulated consistently within a 3-month period. This age group of women is particularly favoured by researchers (see Table 1). Indeed the study conducted by Sutker *et al.* (1987) reported that four women from a study group of 12 had to be excluded due to hormonal evidence of anovulatory cycles.

Investigators have employed different criteria to define the various cycle phases, making inter-study comparisons difficult. For example Sutker *et al.* (1987) defined the mid-luteal phase as days 20–25 while Jones and Jones (1976) defined their pre-menstrual phase as days 21–28.

Many studies have investigated small numbers of women. Cole-Harding and Wilson (1987) studied 32 women, but each subject was investigated at only one of the three phases of the cycle. Freitag and Adesso (1993) reported results from 48 women, but they were 'heavy drinkers' and no hormonal analysis was performed.

The importance of considering inter- as well as intra-individual variations in responses to alcohol cannot be over-emphasized. On the one hand, there are individual variations in the hormonal

patterns during the menstrual cycle, and, on the other, variations in individual responses to alcohol. The 'within-subjects design' has much to commend it; but not all studies employed this procedure. Furthermore Dye (1990) has stressed the importance of controlling for circadian rhythms when investigating menstrual cycle rhythms. In some instances the former can be of greater amplitude than the latter.

The procedure adopted for alcohol administration has varied between studies. Most investigators have administered a dose of alcohol equal to 0.52 g/kg. Sutker *et al.* (1987) investigated the effects of this dose and also a 0.80 g/kg dose. Niaura *et al.* (1987) investigated the effects of a 0.65 g/kg dose of alcohol, while Cole-Harding and Wilson (1987) employed a dose of 0.80 g/kg. The time allowed to consume the drink varied between studies: 1 min in the case of Marshall *et al.* (1983) but one-third of the drink every 20 min in the study of Niaura *et al.* (1987). The extent of fasting before alcohol administration varied. Niaura *et al.* (1987) began testing immediately after a standard breakfast, while Sutker *et al.* (1987) began testing after a 10 h fast.

Three studies (Brick *et al.*, 1986; Niaura *et al.*, 1987; Hay *et al.*, 1984) had significant numbers of contraceptive pill users within their study group (6/10, 7/13 and 11/20 respectively).

It is difficult to address the question of whether the pharmacokinetics of alcohol vary across the female menstrual cycle where the data relating to the blood alcohol measurements are not presented in conjunction with serum hormone determinations made at the various cycle phases. In only two studies (Sutker *et al.*, 1987 and Marshall *et al.*, 1984) was ovulation confirmed by chemical means. In both these studies, a within-subject design was adopted; however, in the latter case, Marshall *et al.* (1983) compared two phases of presumed elevated sex steroids: days 8–10 and days 22–24. By way of a contrast, Sutker *et al.* (1987) studied three cycle phases and included a phase of presumably low hormone levels, i.e. days 2–7. This study of Sutker *et al.* (1987) remains the best piece of research to-date. Their conclusion that women may eliminate alcohol more rapidly during the luteal phase of the cycle merits further investigation. Unfortunately Sutker *et al.* (1987) studied only eight women and future studies should increase the number of subjects, monitor

serum hormone levels at each cycle phase and should study several consecutive cycles.

#### FACTORS WHICH MIGHT INFLUENCE ETHANOL PHARMACOKINETICS IN THE PRE-MENOPAUSAL FEMALE

It is a generally held view that given the same dose of alcohol, women will attain a higher blood alcohol level (BAL) than their male counterparts. Women have a higher proportion of fatty tissue than men and thus lower body water content. Alcohol is therefore less diluted in the female and a standard dose of alcohol will produce a higher BAL than in a male. Another difference between the sexes is revealed when the extent of alcohol breakdown within the stomach is compared. This breakdown, or first-pass metabolism, of alcohol is performed by the enzyme alcohol dehydrogenase. Female levels of this gastric enzyme have been shown to be only 59% of those of males (Frezza *et al.*, 1990). These findings were recorded in women during the 'second half' of the menstrual cycle. It would be of interest to learn whether or not the levels of enzyme fluctuate between the different phases of the cycle, which may consequently affect the pharmacokinetic response of the pre-menopausal woman to alcohol.

The rate of gastric emptying controls the rate of delivery of stomach contents to the small intestine and thereby the rate of alcohol absorption. It follows that any factor which alters the rate of movement of stomach contents through the gastrointestinal tract can affect the rate of alcohol absorption. There is good evidence that the cyclical changes in hormone levels which characterize the menstrual cycle can affect the rate of gastrointestinal transit. For example oestrogens and progesterone may play a role in the pathogenesis of heartburn accompanying pregnancy (Van Thiel *et al.*, 1976; Fisher *et al.*, 1978). A lower oesophageal sphincter muscle pressure was reported during the luteal phase of the menstrual cycle (Van Thiel *et al.*, 1979). Progesterone has been given a causative role in the gall-bladder stasis experienced by some women during pregnancy (Braverman *et al.*, 1980) and during the mid-luteal phase of the cycle (Nilsson and Stattin, 1967). Gastrointestinal transit times may be altered in pregnancy (Wald *et al.*, 1982) and by phase of menstrual cycle (Wald *et al.*, 1981; Gill

*et al.*, 1987); the luteal phase being associated with a prolongation of gastrointestinal transit time. If the female hormones do affect gut motility, it can be anticipated that the rate of absorption of alcohol into the bloodstream will be altered and the available evidence reported above suggests that the luteal phase of the cycle is characterized by a prolongation of gastrointestinal transit time and therefore slowed absorption and hence reduced BALs.

Several parameters relating to the BAL curve may be used by investigators to compare alcohol responses in study subjects; the peak BAL, the time to reach peak BAL, the rate of decline of the BAL curve (i.e. elimination rate) and the area under the BAL curve. The latter measurement gives an estimate of the mean blood alcohol level. Sutker *et al.* (1987) reported that, during the luteal phase of the cycle, the area under the curve was lower. This finding is consistent with the evidence cited above that the luteal phase of the cycle is associated with a prolongation of gastrointestinal transit time.

Changes in the renal handling of alcohol may also be responsible in part for the reported changes in alcohol pharmacokinetics across the cycle. Fiset and Le Bel (1990) reported that the glomerular filtration rate increased during the luteal phase of the menstrual cycle in the absence of consistent changes in urine volume. It may be timely to investigate urinary output of alcohol as a function of menstrual cycle phase.

Jaulmes *et al.* (1956) reported that a reduction in body temperature may retard alcohol absorption. In some women, the luteal phase is characterized by a rise in body temperature.

#### DISCUSSION AND CONCLUSIONS

The fluctuating response of women to a standard dose of alcohol at differing stages of the menstrual cycle reported by Jones and Jones (1976) has not been validated by subsequent studies. Despite the severe methodological shortcomings of this study (failure to establish hormone levels; inadequate method of cycle phase designation; of 20 women tested attendance was only requested at 'two of the three times during the cycle'; six women failed to return for a second session), its results continue, mistakenly, to be quoted widely.

Evidence to date suggests that women may eliminate alcohol more rapidly and also achieve a slightly lower mean BAL during the luteal phase of the cycle. These findings represent data derived from just eight women. Further work is required.

The changes in alcohol pharmacokinetics proposed to occur during the luteal phase of the cycle may be the consequence of a decreased gastrointestinal transit time causing in turn a slowed absorption of alcohol and/or an increased elimination of alcohol via the kidneys. In the former case, it is important to note that the pharmacokinetic study of Sutker *et al.* (1987) was performed on women who had fasted for 10 h. The effect of hormones on the gut transit time of an alcohol solution taken with food may be quite different.

Do the findings of Sutker *et al.* (1987) caution that the health message for women should be modified? Should they be warned that their response to alcohol will vary across the cycle and also, as a consequence, their degree of impairment? Available evidence suggests not, for it must be remembered that the study conditions employed were quite different to the pattern of 'normal' social drinking. The subjects had been fasting for 10 h. A dose of 0.52 g of alcohol/kg was administered. Assuming a body weight of 60 kg, this is equivalent to 31.2 g or just under 4 units of alcohol consumed in 15 min. This is equivalent to a drinking 'speed' of 16 glasses of wine per hour! Before health education messages are modified, the study should be repeated using women investigated under conditions more akin to normal social drinking practices.

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