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LONG TERM EFFECT OF CAFFEINE INTAKE ON SERUM ESTROGEN LEVELS AMONG FEMALES OF CHILD BEARING AGE- A REVIEW

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ABSTRACT

Many studies have indicated that caffeine consumption among women of child-bearing age has its effect on estrogen levels. The variation in estrogen levels associates with disorders such as endometriosis, osteoporosis, endometrial, breast and ovarian cancers. Long term caffeine consumptions potentials to influence estrogen levels over a long period of time and thus it make sense to take caffeine consumption into account when designing studies to understand these disorders. Caffeine, and probably dimethylxanthines, is ergogenic for most of the women. The mechanisms involve in the mode of actions of these compounds are varies and complex and extend well beyond the traditional explanation of sparing of muscle glycogen to probably involve fundamental aspects of muscle contractility. This probability mostly affects the level of estrogen in women especially in women with child bearing age. Caffeine acts as the suppressor for the estrogen hormone. Purpose of this review is to reveal the actual responces of caffeine towards the estrogen hormones.

KEYWORDS: *Estrogen; caffeine; hormonal changes; females; endometriosis;dimethylxanthines*

I. INTRODUCTION

Caffeine is a common substance in the diets of most women and it is now appearing in many new products, including energy drinks, sport gels, alcoholic beverages and diet aids. The sources of caffeine are from the leaves, seeds and fruits more than 60 varieties of plants, including tea, coffee and kola plants [1]. Many companies nowadays are also producing caffeine synthetically. It's a central nervous stimulant; caffeine will be quickly absorbed by the brain and excreted in the urine after many hours. Common nutritional sources of

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caffeine include coffee, tea, chocolate and most colas, as well as some medications. Excessive consumption of caffeine can cause many symptoms of anxiety, insomnia, and nausea and also induce increase in heart rate [2].

Estrogen is the hormone that plays a major role in female reproductive system which act as the guidance. [3]. It is the secondary characteristics that appear during puberty, such as increased breast size and genital hair, result from increased estrogen levels in the female body. During the menstrual cycle, estrogen level in female body rises, it stimulates the maturation of eggs, ovum.[4] If fertilization does not take place, the estrogen levels then decline rapidly during the luteal phase–the last two weeks of the menstrual cycle. Whereas in menopausal female estrogen level will be declined but production never ceases completely.

Studies on fertility and sterility found that estrogen level in women between the ages of 36 and 45 in the first stage of the menstrual cycle increases with more than one cup of coffee a day. In a study reported in the June 2005 issue of "Cancer," caffeine intake decreases the estradiol, one of the estrogen form, during the luteal phase of the menstrual cycle. Both caffeinated coffee and caffeinated tea had this effect. Researchs show that caffeine might inhibits the aromatase, a key enzyme in the production of estrogen in the body[6].

PHARMACOKINETICS

After ingestion, the caffeine will be absorbedrapidly and completely from the gastrointestinal tract into the bloodstream. Maximum caffeine concentrations in blood will reach within 1hour- 1hour 30 minutes after its ingestion. Absorbed caffeine will be completely distributed throughout the entire body. Caffeine has the ability to pass across the blood–brain barrier, also enters amniotic fluid and the foetus through placenta, and also into breast milk. Caffeine is also been detected in the semen[7].

The site ofprimary metabolism of caffeine is in the liver. Caffeine in adult will usually metabolizedcompletely to 1- methylxanthine and 1-methyluric acid from the para-xanthine intermediate. Only 1–5% of the ingested caffeine will be recover unchanged in the urination. Infants up to the age of 8–9 months excrete about 85% of caffeine[8]. They have a great reduced ability to metabolize caffeine.

Half-life eliminating factor of caffeine ranges between 3 and 7h. There are many influencing factors for this such asgender, age, usage of oral contraceptives, pregnancy and smoking habits. When a comparison between the caffeine's half-life in male and female is analysed, it was reported as 20–30% shorter in females. The half-life ofnew-bornsare ranged from 50 to 100 h, but it approaches a gradual of an adult by 6 months of age. In females using oral contraceptive steroids, the caffeine half-life is approximately twice that is observed for ovulatory females. In first trimester, the metabolic half-life increases steadily from 4h to 18h. Cigarette smoking is associated with about a twofold increase in the rate at which caffeine is eliminated.[9]

MODE OF ACTION OF CAFFEINE

Physiological concentrations of caffeine are normally less than 70 µmol/L; plasma concentrations of 20 to 50 µmol/L are common. However, the concentrations employees in most in vitro investigations ranged from 500 to 5000 µmol/L. The physiological factors of such studies is not clear. While certain modes of action for caffeine was identified as the only one important aspect is caffeine inhibits the adenosine receptors in the body[10]. Caffeine has a very similar structure to adenosine and it able to bind with the cell membrane receptors

for adenosine, thus blocking their action[11]. Adenosine receptors are found in most tissues, including the brain, heart, smooth muscle, adipocytes and skeletal muscle. The ubiquitous nature and varies type of adenosine receptor facilitates caffeine simultaneously affects a variety of tissues, resulting in a wide range of often interacting responses.Caffeine also have intracellular actions, but it is not clear whether they effects the enzymes directly or due to post-receptor events. In addition, caffeine also has the characteristic of stimulating the secretion of adrenaline (epinephrine). This response produces a number of secondary metabolic changes that promotes an ergogenic action [12].

DIMETHYLXANTHINES

Most of the researches have explained about the caffeine's unique ergogenic substance which was a controversy. As mentioned above, caffeine is an adenosine-receptor antagonist. The liver demethylates this trimethylxanthine to 3 dimethylxanthines: paraxanthine, theophylline, and theobromine, which will be further catabolisation. In humans, the major product is paraxanthine. Paraxanthine and theophylline are also potent adenosinereceptor antagonists. Metabolism of caffeine usually does not increases the level of paraxanthine and theophylline in the circulation to a concentration considered active[13]. They are therefore unlikely to be of major consequence to the effects of caffeine. However, they can be prepared and used as drugs. Paraxanthine is not biologically available and is not prepared commercially as a pharmacological product. Theophylline is a major component of tea and is a common drug which has few similarities of pharmacodynamic actions as caffeine. Marsh et al.[14] reported an ergogenic effect of theophylline in a study involving only 3 participants and, recently, theophylline was found to increase endurance to a similar extent as caffeine. Because paraxanthine is also likely to be an ergogenic aid, dimethylxanthines in general should be considered performance enhancing drugs and should therefore probably be regulated.

ESTROGEN LEVEL

Many studies had indicated that caffeine consumption among women of child-bearing age influences estrogen levels. The variations in estrogen levels associates with disorders such as endometriosis, osteoporosis, and endometrial, breast, and ovarian cancers. Due to long term caffeine consumptions, the potentials to influence estrogen levels over a long period of time, make sense to take caffeine consumption into account when designing studies to understand these disorders.[15]

The varies pathophysiologic factors effecting estrogen level due to caffeine and components of caffeinated beverages on estrogen hormones and ovulatory malfunction exist. Caffeine is associated with estradiol and other hormone alterations which affects the ovulation. A shorter menstrual cycle length and a long menstrual cycle length has also been related to caffeine consumption.

Animal models suggest that caffeine can be inhibited by oocyte maturation or enhance steroids production via inhibition of phosphodiesterase.Alternatively, it interferes with estrogen metabolism via inhibition of aromatase (key enzyme responsible for converting androgens to estrogen). Many studies shows women suggest that caffeine may have a positive, inverse, or null association with E24, but has no effect on ovulatory function, although no studies to date have prospectively measures caffeine intake at multiple time points and directly measured ovulation. The hepatic enzymes CYP1A2 metabolises both caffeine and E2.

Polymorphism of CYP1A2 links to variables in caffeine clearance and serum E2 concentrations and shows to modify relations between caffeine intake and adverse health outcomes[16].

Estrogen and caffeine metabolism and risk of breast and ovarian cancers have also been shown to differ between whites and Asians [17]. It is unknown whether differences in caffeine consumption and metabolism could partially explain these differences.In pre menopausal women at higher risk of breast cancer,there are chances of reducing it by 25-70% with daily consumption of 4-6 cups of coffee drinkers daily than non coffee drinkers [18]. IPrimary objectives of this review were to determine whether caffeine and its associated beverages (coffee, tea, and soda) are related to serum concentrations of reproductive hormones mainly of estrogen levels in body. The secondary objectives were to determine whether caffeine and its associated beverages are associated with incident of anovulation.

REPRODUCTIVE AND DEVELOPMENTAL EFFECTS

There are many evidences that proved women have spontaneously reduces their caffeine intake during pregnancy.. Nevertheless, consumptions of caffeine in this group can retain relatively high. About 98% of women of child bearing age has regularly consumes caffeine in the form of beverages or in caffeine-containing medications, while about 72% of women reported to continue with caffeine consumptions during pregnancy . Many epidemiological investigations reported show that majority of women consumes caffeine during pregnancy in a range of 100– 300 mg day 1. In the other hand, a small proportion of women in population ingest a larger amount of caffeine which is 5400 mg caffeine per day.

In the past 20 years, evidences have accumulates theconcern effects of caffeine consumptiononreproductiveand pre andpostnatal developmental. Some bulk of evidences suggestedcaffeine intake at dose levels of 5300 mg per day may leads to adverse effects on some reproductive and developmental parameter when exposal take place during certain periods.

The caffeine effects on the outcome of pregnancy appear to be biologically plausible. So many published data proved that the human foetus and neonate leads to exposal of substantial amounts of caffeine or its metabolism. Caffeine is rapidly absorbed from the mother’s gastrointestinal tract, which crosses the placenta and distributed to all foetal tissues, includes the central nervous system. In addition, exposal of the foetus and newborn to caffeine enhance due to half-life of caffeine being markedly increases oxidation of methylated xanthines.[19]

EFFECTS ON CONCEPTION AND FEMALE FERTILITY

Factor implication reduces the fecundity, or the capacity to reproduce. Caffeine could delay conceptionsin several plausible biological mechanisms. Caffeine consumptions will alter hormone level, endometriosis, associates with tubal transport time, and with reductionof viability of fertilized ovum .Caffeine metabolism during the menstrual cycle, will reduce clearance during the luteal phase, the larger accumulation during the period of implantation and early embryonic developmental phase. Caffeine consumption leads to miscarriage, which might result in prolonged of the waiting time requiresachieving a clinically recognized pregnancy.

Thirteen epidemiological studies, data collected retrospectivelyand prospectively investigate the relationship between caffeine consumption and time to fecund ability present conflicting results. Five studies reviewed have no delay in conceptions in women who consumed up to 5 700 mg caffeine per day before pregnancy. In a multicentre studies conducted a particular area, caffeine consumption was not associate with fertilities group of 2817 women whose caffeine consumption from all sources ranged from 100 to 5 240 mg per day. Some research has shownthere are no association between subfecundity and consumption of coffee or tea at any dose level (none to eight cups per day) among non-smoking women. However, the caffeine intakes of a mean dosage level of about 90 mg per day associates with reduction in fertility[20].

Moreover, a significant decreases in monthly probability of pregnancy among women who consumes the equivalent of three or more cups of coffee per day (5300 mg caffeine per day).

In a retrospective studies, reported that delay conceptions in women is seen who consumes 5400, 5500, or 5800 mg caffeine per day. The dose-related effect of coffee consumption on reports difficulties in becoming pregnant. Women who were heavy caffeine consumer before pregnancy experiences almost double the time in becoming pregnant compared with women who don't consumed.[21]A large cross-sectional study on 3010 postpartum women, reported that time to conception for women who consumed three, two, one or no cups of coffee per day were same (ranging from 4.8 to 5.0 months), whereas time to conception was longer (6.6 months) for women who consumes four or more cups of coffee per day (approxi- mately 400 mg caffeine per day). Women in this highest level of consumption had an increase of 11% in the time leading to the first pregnancy. (The effect of drinking >500mg caffeine day 1 was rela- tively stronger in smokers [OR 1⁄4 1.56, 95% CI 1⁄4 0.92–2.63] than in non-smokers [OR 1⁄4 1.38, 95% CI1⁄40.85–2.23].) In Olsen (1991), a statistically significant association was observed (OR 1⁄4 1.35, 95% CI 1⁄4 1.02–1.48) for a delay of 5 1 year in women who smoked and also consumed at least eight cups of coffee per day (or an equivalent amount of caffeine from 16 cups of tea).

Three studies found modest positive associations with delayed conception from maternal consumption of more than one caffeinated beverage per day. A pro- spective study by Wilcox et al. (1988) showed that women who consumed more than one cup of coffee per day (126mg caffeine day 1) were half as likely to conceive during a given menstrual cycle. In a cross- sectional study, Hatch and Bracken (1993) found that intake of caffeine from coffee, tea and caffeinated soft drinks was associated with an increased risk of a delay of conception of 5 1 year. Compared with no caffeine use, consumption of 1–150 mg caffeine day 1 resulted in an OR for delayed conception of 1.39 (95% CI 1⁄4 0.90–2.13), consumption of >300 has 27% of low conceiving for each cycle. Women who reported drinking >300 mg caffeine day 1 had a 27% lower chance of conceiving for each cycle, and those who reported drinking <300 mg day 1 had a 10% reduction in conception rates per cycle compared with women who consumed no caffeine. Hakim et al. (1998) examined the effects of caffeine consumption on con- ception in a prospective study of 124 women, finding that the consumption of the equivalent of more than one cup of coffee per day among the sample of women who neither smoked nor drank alcohol was associated with a decreased risk of conception (18.0%, adjusted OR 1⁄4 0.56, 95% CI 1⁄4 0.23–1.33), which did not reach statistical significance[22].

In one of the above-described studies, delayed con- ception was observed among non-smoking women who consumed >300 mg caffeine day 1 , but not among women who smoked (Stanton and Gray 1995). Also, Jensen et al. (1998) found no dose– response relationship among smokers at caffeine doses of up to 5 700 mg day 1, whereas non-smoking males and females who consumed 300–700mgday 1 exhibited decreased fecundability compared with non-smoking couples with caffeine intake of <300 mg day 1. However, in Olsen (1991), no asso- ciation was found among non-smokers at any dose level of caffeine, just for women who smoked and also consumed at least eight cups of coffee per day. Bolumar et al. (1997) also found that the effect of drinking >500 mg caffeine day 1 was relatively stron- ger in smokers than in non-smokers. An interaction between caffeine and smoking is biologically plaus- ible. Reports in the literature have shown that cigar- ette smoking significantly increases the rate of caffeine metabolism (see 'Pharmacokinetics'). The enhanced caffeine metabolism in smokers also accelerates caf- feine clearance and, as a result, reduces the duration and magnitude of the exposure.[23]

Most epidemiological studies reviewed here were affected by methodological issues, including inade- quate measurement of caffeine intake, failure to dis- tinguish among different types of preparation and different strengths of coffee, inadequate control for possible confounding effects, recall bias in retrospec- tive studies, lack of data on frequency of unprotected intercourse, and, in some studies, inadequate sample size. Despite these limitations, epidemiological studies are an important source of information on potential adverse effects of caffeine on fertility (delayed conception) in humans..

SPONTANEOUS ABORTION (MISCARRIAGE)

The influence of caffeine on the risk of spontaneous abortion in humans is difficult to assess. A number of studies have been conducted that show either a positive effect or a lack of effect of caffeine on this pregnancy outcome. Shortcomings in the literature include small sample size and inadequate adjustmentfor potential confounders.[24]

A major potential confounder is the presence of nausea in the first trimester of pregnancy, as a lack of nausea early in pregnancy has been associated with a significantly increased risk of miscarriage (Stein and Susser 1991). Nausea in pregnancy may cause a reduction in the consumption of coffee/caffeine, while a lack of nausea may lead to continued ingestion. This may result in an erroneous association of caffeine intake with increased risk of spontaneous abortion[25]. Another drawback is the general lack of accurate measurement of actual caffeine consumption by the participants in the epidemiologi- cal studies. Stavric et al. (1988), for example, found a marked variation in caffeine content of coffee and tea depending on the method of preparation and brand, and errors also arise from differences in the size of the serving 'cup' used by different participants[26]. Another serious limitation is the potential for poor identifica- tion of foetal loss due to enrolment of women later in the pregnancy or only those who presented to hospi- tals, as many early foetal losses go unnoticed by women. Studies measuring human chorionic gonado- trophin levels, such as those of Wilcox et al. (1990), Mills et al. (1993) and Hakim et al. (1993), should reduce any bias in this factor. In addition, the ma- jority of the studies showing positive associations between caffeine and spontaneous abortion are retrospective in nature, and at least one study de- pended on information recalled after several preg- nancies (Armstrong et al. 1992)[27].

Most of the studies have shown no association be- tween a caffeine intake of <300 mg day 1 and an increased risk of spontaneous abortion [28](Watkinson and Fried 1985, Wilcox et al. 1990, Armstrong et al. 1992, Mills et al. 1993, Dlugosz et al. 1996, Wen et al. 2001). In the one study that accurately assessed caffeine intake (the prospective study by Watkinson and Fried 1985), 284 mothers were interviewed about their caffeine intake from coffee, tea, caffeinated soft drinks, chocolate bars, [29]chocolate drinks and caffeine- containing medicines 3 years before pregnancy, dur- ing each trimester of pregnancy and the year after pregnancy. Caffeine consumption was measured and categorized into <100, 100–300 and >300 mg day 1 . There was no association between caffeine consump- tion and risk of miscarriage[30]. In this study, there was a long period for which the women had to recall their caffeine consumption, so all recalled intakes may not have been accurate. Another study that found no association between caffeine consumption at levels of 5 300 mg day 1 and an increase in spontaneousabortion was the prospective study by Mills et al. (1993)[31].

II. CONCLUSION

Caffeine, and probably dimethylxanthines, are ergogenic for most of the women. The mechanisms involve in the mode of actions of these compounds are varies and complex and extend well beyond the traditional explanation of sparing of muscle glycogen to probably involve fundamental aspects of muscle contractility[32]. This probability mostly affects the level of estrogen in women especially in women with child bearing age. Caffeine act as the suppressor for the estrogen hormone. Many scientists have conducted very descriptive investigations. They should recognise that the effects of caffeine are also demonstrating the consequences of antagonising normal biological function and, as such, may reveal important aspects of physiological regulation[33]. Such results may well have wider implications and apply to both basic and medical sciences[34].

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