

MEETING REPORT

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## Caffeine, Alcohol, and Psychological Stress and In Vitro Fertilization

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**Abstract:** There has been an astounding explosion in the number of clinics offering ART techniques- 426 program in the US and 600 in Europe. Despite enormous advances regarding the technical aspects of the IVF procedure, the parents' contribution has virtually been ignored. What is reassuring for patients is that lifestyle habits are within the patient's control, and when modified, could lead to healthy babies. The focus of this paper will be on the current state of knowledge about the effects of female and male caffeine and alcohol use, and psychological stress on the reproductive endpoints of IVF. There is currently only one study on the effects of caffeine on IVF. In this study, caffeine intake by women had a profound effect on: 1) Miscarriages, 2) Not achieving a live birth and 3) Infant gestational age. The findings of this study require further confirmation. Success rates may be further affected by alcohol consumption. Female alcohol use was associated with: 1) A decrease in number of oocytes aspirated, 2) Not achieving a pregnancy, and 3) Increased risk of miscarriage. Male alcohol use was associated with: 1) Spontaneous miscarriages, and 2) Not achieving a live birth, particularly if consuming beer. Stress also has an impact on IVF success rates. There are several statistically significant studies on baseline and procedural depression, anxiety, stress, and mood, as well as stress hormones that all negatively affected pregnancy rates after IVF. However, the literature on stress and ART was devoid of an instrument that captures the female and male experience of going through ART. Thus, an instrument was developed that rated concern levels about anesthesia, surgery, pain, recovery time, side-effects, finances, missing work, insufficient information and delivering a healthy baby. At baseline, women who were concerned about the medical aspects of the procedure had fewer oocytes retrieved and fertilized. For women concerned about missing work, they had over twice the risk of not achieving a pregnancy, while women extremely concerned about finances had a very high risk of no live birth. Understanding both the independent and combined effects of stress, alcohol, and caffeine on ART may ultimately lead to effective interventions that will decrease adverse outcomes and in turn, produce healthy babies that mature into healthy children and adults.

**Keywords:** in vitro fertilization, caffeine, alcohol, psychological stress, assisted reproductive technologies, lifestyle habits, gamete intrafallopian transfer

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## Overview

Are any major lifestyle changes necessary while undergoing assisted reproductive technology treatments? In assisted reproductive technology, we take such control over the whole reproductive process that major changes in lifestyle are not necessary. We are in control over the ovaries, how quickly the eggs grow and how they are fertilized in the laboratory. It seems quite difficult to understand how any lifestyle change could possibly impact that technique. It is easy to be dazzled by the high pregnancy rates of ART programs.<sup>1</sup>

There has been an astounding explosion in the number of clinics offering ART techniques. In the US there are currently 426 programs, with an additional 600 programs in Europe.<sup>2</sup> ART is a multi-billion dollar industry which fulfills the dream of every infertile couple, to have a healthy baby. The current live birth success rate after using ART in the US is 30%.<sup>3</sup> This has exceeded natural fecundity (reproduction) which promises a 25% chance of achieving a pregnancy each cycle. Both these averages are considerably higher in Europe, where the live birth delivery rate is 17.4%.<sup>2</sup>

Since the advent of ART, researchers and clinicians are still grappling to identify factors other than female age, causes of infertility, culture medium, number of embryos transferred quality of sperm and response to hormonal stimulation and cryopreservation which may affect success rates.

Despite enormous advances regarding the technical aspects of the IVF procedure, the parents' contribution has virtually been ignored. It has taken over 15 years to convince reproductive endocrinologists that lifestyle habits may play a significant role on ART endpoints—yet, most are still skeptical. Meanwhile, every group of doctors continues to strive for an extra 1%–2% increase in pregnancy rates to confirm their excellence in the field of reproductive endocrinology.

What is truly exciting about IVF is that it provides a physiological window to view the effect of each lifestyle habit on the sperm and the egg. It also provides the opportunity to focus on the male and his contribution towards adverse outcomes of ART. We have optimized our control over reproductive technology, but have not addressed some of the most important issues.<sup>4</sup> We are dealing with women and men who drink coffee or alcohol, or are under stress but still want that “perfect baby” while undergoing

ART, yet these habits may reprogram the developing ovary from achieving its optimal potential. To date, there is a tremendous scarcity of evidence of the health risks of these substances on IVF outcomes.

Amazingly, The American Society for Reproductive Medicine currently has guidelines in the United States to limit the number of embryos transferred (ET) (i.e. <35 years  $n = 1-2$  ET; 38–40 years  $n = 3$  ET, and >40 years  $n = 5$  ET).<sup>5</sup> Remarkably, in 2009, there are still no recommendations regarding the indulgence or modification of lifestyle habits, which could possibly enhance assisted reproductive technology (ART) success rates.

What is reassuring for patients is that lifestyle habits are within the patient's control, and when modified, could lead to healthy babies. Hence, today, I will focus on the current state of knowledge about the effects of female and male caffeine and alcohol use, and psychological stress on the reproductive endpoints of IVF.

## Caffeine Consumption and IVF/GIFT

Caffeine is one of the most widely used pharmacologically active substances in the world—it is a household habit. >500 billion cups of coffee<sup>6</sup> are consumed every year worldwide. Most prospective couples are aware that alcohol use may be detrimental to pregnancy; however, caffeine use is readily accepted by couples trying to achieve a pregnancy. Interestingly, 80% of pregnant women consume caffeinated beverages.<sup>7</sup>

To date, there is only one study that has investigated the effect of caffeine consumption by men and women on success rates of IVF.<sup>8</sup> We recruited a total of 221 couples undergoing IVF or GIFT from 7 centers in southern California. These centers were chosen because of the physicians' expertise and uniformly high success rates. This was a multi-center prospective study.

The eligibility criteria consisted of the following: 1) Couples with primary or secondary infertility due to tubal disease, endometriosis, immunological causes, male factor, or unexplained infertility were selected; 2) All patients were >20 years; 3) Had undergone an evaluation for infertility, such as a laparoscopy, hysteroscopy, semen analysis and sperm penetration assay; 4) Had a stable relationship; and 5) Women with pre-existing illness (e.g. high blood pressure, heart, thyroid or renal disease, diabetes) were excluded.



In addition, couples using donor sperm, oocytes, or surrogate uteri were also not included because of the absence of an accurate lifestyle history. Finally, only one cycle/couple was included during the study, since lifestyle habits remain constant over several attempts.

For all men and women, we collected information on the type, timing, and amount of caffeine. The sources of caffeine came from caffeinated or decaffeinated coffee, tea, soda, cocoa drinks, or chocolate bars. The amount of caffeine was tabulated on the number of cups, glasses or ounces/day during specific time periods. Usual caffeine intake was calculated at 4 time points: 1) during the person's lifetime; 2) 1 year prior to the attempt; 3) during the week of the initial clinic visit; and 4) during the procedure.

Male and female caffeine intake was converted to exact amount in milligrams. Briefly, 1 cup coffee has about 100 mg of caffeine, a cup of tea or can of soda was 50 mg/cup/can, while 1 oz of dark chocolate is about 18 mg and milk chocolate was 7 mg. In addition, 1 cup of hot cocoa was 4 mg/cup, and decaffeinated tea, coffee, and soda were estimated at 2 mg/cup or glass. For each time period the total amount of caffeine was calculated by adding the amounts consumed from all food products.

There were a total of 5 self-administered questionnaires. Women completed three questionnaires; specifically during the first clinic visit, during the week of the procedure, and at the pregnancy outcome, while men completed two questionnaires: during the first clinic visit and at the time of sperm collection.

## Female Caffeine Intake and IVF Outcomes

In this study, caffeine intake by women had a profound effect on: 1) Miscarriages, with OR ranging from 6.2 to 19.8, depending on the amount and timing of caffeine consumption, 2) Not achieving a live birth (from not becoming pregnant or experiencing a miscarriage), with OR ranging from 2.9 ( $P = 0.01$ ) to 3.9 ( $CI P = 0.01$ ), and 3) Infant gestational age, which decreased from 3.5 to 3.8 weeks based on 41 live births for  $>50$  mg. caffeine.

For miscarriages, it should be noted that the sample sizes were small ( $n = 21$ ), the confidence intervals were very wide, so the magnitude of association for caffeine and miscarriage may be unreliable.

## Male Caffeine Intake and IVF Outcomes

On the other hand, male caffeine intake did not affect any sperm parameters, embryo transfer, pregnancy, live birth or neonatal characteristics. However,<sup>1</sup> Increases of an extra 100 mg/day (1 extra cup of coffee) for usual caffeine intake by men increased the risk of multiple gestations by 2.2 (0.02) for lifetime use of caffeine, and by 3.0 times ( $p = .0$ ) during the initial clinic visit, based on 19 multiple gestations and 71 pregnancies.

## Caffeine Summary

This was the first study to report any effect of caffeine on live births, miscarriages, and gestational age in women, and multiple gestations in men. The findings of this study require further confirmation. The body of evidence for an association between caffeine and IVF is inadequate at present due to the scarcity of studies.

There were several limitations in this study: First, it is impossible to determine exactly how much caffeine was present in a cup of coffee or tea. The amount depends on the mix of the brew, how it is prepared, and the size of the cup. Next, serum concentrations of caffeine or its primary metabolite, paraxanthine were never measured. Furthermore, caffeinated drugs (e.g. Excedrin, Fiorinal) and dietary supplements were not tabulated in this data set. Finally, the study population is predominantly White and well educated. They were however, representative of all women undergoing ART in southern California.

One of the latest studies to ponder the effect of caffeine on fertility and pregnancy consists of a recent study<sup>9</sup> presented to ESHRE in 2008. The researchers tracked down the dietary habits of 9,000 women undergoing IVF from 1985–1995 in the Dutch town of Nijmegen, to gauge their likelihood of naturally conceiving a child. About 1 in 7 of the subject group became pregnant naturally, with 45% expecting within 6 months of their last IVF session. But among women who drank  $\geq 4$  cups of coffee/day, the likelihood of becoming pregnant fell by 26%. This suggests that infertility patients should cut back on caffeine intake to increase their chances of conceiving. The final recommendation was that “patients may influence their chance of spontaneous pregnancy after IVF with a healthy lifestyle.”



## Alcohol Consumption and IVF/GIFT

Success rates may be further affected by alcohol consumption. A total of 2 billion people across the world consume alcoholic drinks<sup>10</sup> Furthermore, adults consume an average 11 L of pure alcohol from beer, wine, and liquor/ year.<sup>11</sup> The highest average alcohol consumption in the world is in Europe (followed by the Americas, and then Africa)<sup>12</sup> (WHO Global Status report on Alcohol 2004). Men and women of reproductive age are the segment of the population most heavily involved in substance abuse. A total of 11% of pregnant women consume alcohol, and 5% are heavy drinkers.<sup>13</sup>

Only one study to date has examined the effect of female and male alcohol consumption as a risk factor for IVF success rates.<sup>14</sup> This prospective study was based on the same 221 couples with the identical inclusion and exclusion criteria as the caffeine study. The primary endpoint was live births, and the secondary endpoints were sperm parameters, oocytes aspirated, embryo transfer, pregnancies and miscarriages. Women ranged from 26–49 years of age, and men from 22 to 55 years. A total of 77% of subjects were white. The majority had completed college and was employed. The average period of infertility was 4 years.

Alcohol use was categorized based on type, amount and time period, and was ascertained in the past (1 year, 1 month, 1 week, and 1 day before ART, and present (first clinic visit, week and day before the procedure, and during pregnancy). The type of alcohol consisted of mixed drinks, wine, beer, and liquor. The amount of alcohol was based on the number of drinks/day or week. Alcoholic beverage consumption for both partners was recorded in grams as well as in of glasses or bottles. Mixed drinks were assigned 11 g. of alcohol per drink, wine was 13 g per glass, beer 5 g per can, and liquor 7 g per glass, respectively. The total grams of alcohol consumed during specified time periods was analyzed as both a continuous and categorical (none,  $\leq 12$  g/d, or  $>12$  g/d) variable. For one drink, the average alcohol intake is 12 g. Continuous predictors were preferred because 1) they captured the linear trend; 2) they did not require arbitrary cutoff values; and 3) odds ratios could be obtained at any increment.

Among women, 95% of patients reported drinking alcohol at some time in their lifetime.

69% of women reported drinking 1 year before the procedure (MEAN = 7 g/d). This decreased to 26% one week prior to the attempt, and to only 6% during the procedure. For all time periods, wine was the most popular beverage for women. Among the male participants, 99% reported drinking alcohol at some time in their lifetime. Approximately 78% of them men consumed alcohol one year before, which fell to 56% 1 week before the attempt (mean, 12 g/d); and finally, down to 19% (20 g/d) the day before the procedure. A total of 41% (16 g/d) of men drank during the IVF procedure, compared to 6% of women. For men, beer was the preferred beverage.

## Female alcohol use was associated with

1. A 13% ( $p = 0.02$ ) decrease in number of oocytes aspirated, when drinking 12 g more/day (which is 1 additional drink), 1 year before the IVF or GIFT attempt.
2. 2.86 times the risk of not achieving a pregnancy ( $p < 0.050$ ), when consuming 12 g more of alcohol per day, 1 month before the attempt and
3. Last of all, 2.21 times an increased risk of miscarriage (when drinking 12 g more alcohol/day), 1 week before the procedure ( $P = 0.03$ ).

Female wine consumption was associated with 4.52 X the risk of no pregnancy when consuming 12 g more/day 1 month before the attempt. One week before the attempt, OR rose to 5.77 for wine and 4.14 for alcohol, but they were not significant due to small number of drinking women.

## Male alcohol use was associated with

1. Spontaneous miscarriages, which increased from OR's of 2.7 to 38.4 when men drank 12 g more/day during any time period. For example, 1 month before the IVF attempt, the OR was 2.70 ( $p = 0.05$ ), 1 week before, the OR was 3.99 ( $p = 0.04$ ), during the first week of the attempt it increased to 5.97 ( $p = 0.02$ ), and the week before sperm collection it was 38.04 ( $p = 0.01$ ).
2. Not achieving a live birth, which was consistently higher when the male partner drank 12 g more/day. The risk went from 2.28 (1 mo prior to the procedure) all the way to 8.32 (wk. before sperm collection).



3. Not achieving a live birth decreased by 5.49 (1 month prior) to 45 times (week before sperm collection), with one additional can of beer/ day, depending on the time periods of consumption.

Live births may have been influenced by the risk of miscarriage. All OR were adjusted for male smoking, either men's or women's age, race, yrs of education, parity, indications for infertility, type of procedure, and number of attempts.

### Alcohol Summary

Limitations were as follows: 1) There appears to be no satisfactory way to avoid the inherent bias in questionnaires- One year, 1 month, and 1 week are fairly gross estimates that are subject to recall bias. 2) Self-reports of drinking may have been underestimated because of fear of social desirability or medical disapproval. 3) Although very few women reported drinking after the procedure and during the pregnancy, a high percentage of men drank alcohol for all the time periods, suggesting a misconception that men's alcohol use does not affect pregnancy rates. 4) Data on male alcohol consumption during the day of sperm collection were not collected. 5) Numbers were too few to evaluate the timing of alcohol use on prolonged labor, birth defects, or low birth weight; these relationships should be examined in the future.

The body of evidence for the effect on ART success rates is insufficient at this time because of the lack of studies on this topic, and the small number of patients consuming alcohol during the procedure. At this time, based on this study, it may be prudent to recommend reducing alcohol for <1 month before starting ART to maximize success rates. This is based on alcohol use 1 month prior and an 1) odds ratio of  $2.86 \times$  risk of no pregnancy in women; 2)  $2.70 \times$  risk of miscarriage in men; and 3)  $5.49 \times$  risk of no live birth with beer consumption in men.

### Psychological Stress and IVF/GIFT

Does psychological stress cause ART failure? Or, does ART failure cause psychological stress? Which is cause and which is effect?

How stressful is IVF? Daily hormone injections, frequent visits for blood tests and ultrasounds, and a surgical procedure to extract eggs may be stressful for a couple who have just finished an infertility work up.

So what is the relationship between stress and IVF and does psychosocial stress have any impact on the outcome? There are a total of 7 studies that have investigated the effects of male stress on sperm parameters. A total of three<sup>15-17</sup> found a relationship between male stress and decrease in semen quality (morphology). The fourth<sup>18</sup> reported lower sperm density, sperm count, and sperm motility. Contrary to this, there were 3 negative studies. One study<sup>19</sup> reported no difference in semen quality, whereas the other two studies<sup>20,21</sup> reported no differences in sperm motility. So in summary, 1) sperm morphology may be an important factor when reporting male stress.

Current studies have reported statistically significant effects of stress on number of oocytes retrieved, fertilization, embryo transfer, and implantation rates. Only one study by us (2001) reported a relationship between baseline affect on oocyte retrieval. A further 3 studies reported that procedural anxiety decreased fertilization rates.<sup>22-24</sup> Our study also reported significant effects of procedural mood (depression and hostility) on embryo transfer. Finally, one study by Gallinelli<sup>25</sup> reported the effects of procedural anxiety on a decreased implantation rate.

Eleven studies<sup>26-36</sup> looked at primarily one endpoint—"achieving a pregnancy," apart from Demyttenaere 1992<sup>27</sup> who looked at pregnancy and spontaneous abortion, and our study<sup>24</sup> that reported on 6 endpoints.

### In Summary

There were several statistically significant studies<sup>22-36</sup> on baseline and procedural depression, anxiety, stress, and mood, as well as stress hormones that all negatively affected pregnancy rates. One prospective study by Anderheim<sup>37</sup> who used the Psychological General Well-Being Index (rather than Beck Depression Inventory or State Trait Anxiety Inventory) during the first IVF treatment, on 166 women, found no effect of stress on pregnancy outcome.

Our study also examined the effect of stress on spontaneous abortion, live birth delivery, as well as neonatal characteristics. We found no effect of psychosocial stress on spontaneous abortion; however Demyttenaere did (baseline depression). We also found an effect of baseline anxiety and affect on live birth delivery rates and neonatal characteristics, specifically low birth weight and multiple gestations). Differences in



the results are primarily due to: 1) Differences in study populations; 2) Quality of self-reporting; 3) Types of stress instruments (Specific standardized, valid, and reliable) and 4) Different IVF endpoints.

At this time, the evidence for an association between stress and IVF outcomes is suggestive but insufficient (based on IOM) due to the paucity and heterogeneity of studies.

## Concerns about Reproductive Technology Instrument

It became apparent after summarizing the literature on stress and ART that the field was devoid of an instrument—that captures the female and male experience of going through ART.

Thus, we developed and administered a scale to 151 women undergoing IVF/GIFT in California who rated concern levels about anesthesia, surgery, pain, recovery time, side-effects, finances, missing work, insufficient information and delivering a healthy baby.<sup>38</sup> Validity was assessed by comparing CART to the Infertility Reaction Scale and Bipolar Profile of Moods States. Factor analysis identified 3 domains: medical concerns; missing work; and having a healthy baby.

At baseline, women who were concerned about the medical aspects (i.e. side effects, surgery, anesthesia, not enough information, pain, and recovery) of the procedure had 20% fewer oocytes retrieved and 19% fewer oocytes fertilized, while simultaneously adjusting for female age, race, education, smoking status, parity, type of assisted reproductive technologies (ART) procedure (IVF or GIFT), type of infertility, and number of previous attempts.<sup>39</sup>

Women who were very concerned about missing work had 30% fewer oocytes fertilized. For women who were moderately concerned about missing work, they had 2.83 times the risk of not achieving a pregnancy. Finally, women who were extremely concerned about the finances had over 11 times the risk of not having a successful live birth delivery.<sup>39</sup>

There is a need for methodologically sound studies that: 1) investigate healthy live birth delivery and neonatal characteristics, 2) consider procedural vs. lifetime stress, 3) include a wider array of psychosocial factors, 4) consider other lifestyle habits, and 5) assess both the sex and steroid hormones at various time points during the procedure.

## Overall Summary

In summary, both female and male habits have an effect on IVF outcomes.

FOR WOMEN: Alcohol consumption was associated with: the number of oocytes retrieved, pregnancy rates, and spontaneous abortions. Interestingly, female stress affected nearly all endpoints, including decreased fertilization, lower pregnancy rates, spontaneous abortions, no live birth deliveries, as well as with low birth infants, and multiple gestations. Surprisingly, female caffeine consumption had an effect on miscarriages, live birth deliveries, and infants with decreased gestational age.

FOR MEN: Alcohol consumption negatively affected achieving a live birth, while caffeine consumption resulted in an increased number of multiple gestations.

Lifestyle research is three dimensional—based on multiple endpoints along the IVF continuum, multiple lifestyle habits, and gender. At this time, more collaborative international research is necessary to confirm relationships about lifestyle habits and ART outcomes. Understanding both the independent and combined effects of stress, alcohol, and caffeine on ART may ultimately lead to effective interventions that will decrease adverse outcomes and in turn, produce healthy babies that mature into healthy children and adults.

## Disclosure

The authors report no conflicts of interest.

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