REVIEW ARTICLE

Prevailing knowledge about Male and Female lifestyle habits and In Vitro Fertilization in the 21st century

Hillary Klonoff-Cohen, PhD

Affiliation:
University of Illinois at Urbana-Champaign

Corresponding author:
Hillary Klonoff-Cohen, PhD, Saul J. Morse & Anne B. Morgan Professor in Applied Health Sciences; Director, MPH Program; Associate Head for Community Health, Department of Kinesiology and Community Health,
University of Illinois Urbana Champaign, 1206 S Fourth Street, Champaign, IL 61820
E-mail: klonoffc@illinois.edu, 217-244-6242

ABSTRACT

At least one million infants have been born in the United States with the help of in-vitro fertilization (IVF) or other assisted reproductive technologies. Lifestyle factors including smoking, alcohol, recreational drugs, stress, lack of physical activity, and obesity in men and women, which may profoundly influence IVF success rates. Nevertheless, many women and men about to undergo fertility treatment make poor lifestyle choices that may possibly affect their chances of becoming pregnant. A follow-up systematic review was conducted in PubMED (MEDLINE) from 2005-2017 to evaluate the effects of male and female lifestyle habits on success rates of IVF. There was strong evidence that smoking affects almost every endpoint of IVF. There is also mounting evidence that obesity profoundly affects pregnancy, live birth rates, and is also associated with cancelled cycles. The literature on stress and IVF continues to be contradictory. The results were almost equally divided between four studies that found a negative effect of stress on number of oocytes, embryo transfer, and pregnancy, and three studies that reported no effect on IVF outcomes. The evidence for an association for exercise, alcohol, caffeine, and recreational drugs and IVF is inadequate based on a paucity of studies. In order to resolve this dilemma, national or international databases could be used to effectively and accurately capture lifestyle habits over time on thousands of couples undergoing IVF. This information could eventually help create guidelines for primary care physicians, specialists, and infertile patients. From a medical standpoint, it is probably advisable for men and women contemplating IVF to be encouraged to engage in healthy lifestyles. At this time, a structured educational program, ongoing wellness support, and therapeutic interventions (e.g., smoking cessation, relaxation techniques, substance abuse counseling) could be part of the comprehensive care received at fertility clinics in order to promote healthy lifestyle changes.

Running Title: Lifestyle habits and IVF

1. INTRODUCTION

Medical history, age, quality of oocytes, previous pregnancy history, type of fertility problems, physician expertise, and fertility center success rates are important factors in the field of assisted reproductive technologies (ART).[1] Additionally, lifestyle factors including smoking, alcohol,

recreational drugs, stress, lack of physical activity, and obesity in men and women may also profoundly influence IVF success rates. These health behaviors are important since they are modifiable, and if optimized, may result in an increased probability of successful IVF. As a byproduct, healthy lifestyle habits may also result in an enhanced quality of life and life span.

Nevertheless, many women about to undergo fertility treatment make poor lifestyle choices that possibly affect their chances of becoming pregnant. It has been reported that women engage in high rates of alcohol and caffeine consumption and do not change their exercise levels or body mass index prior to undergoing fertility treatments.[2]

It is important for primary care physicians (including family physicians, internists and obstetricians) who are often the primary gatekeepers of medical care, as well as reproductive endocrinologists, to understand which lifestyle behaviors have the greatest negative impacts on IVF. This paper summarizes the prevailing knowledge in the 21st century about the effects of male and female lifestyle habits on all of the biologic and clinical endpoints of IVF.

1.1. Overview of IVF

At least one million infants have been born in the United States with the help of in-vitro fertilization (IVF) or other assisted reproductive technologies, according to the latest report by the U.S. Society of Assisted Reproductive Technology (SART).[3] The overall success rate for assisted reproductive technologies is 32 percent.[3] The use of ART has doubled over the past decade.[3] Today, approximately 1.6% of all infants born in the United States annually are conceived using ART.[3] Nationally, a "fresh" IVF cycle with medications costs $15,000-$20,000 on average.[4]

IVF (in vitro fertilization) is the most common and effective form of ART. It can used to treat patients with blocked or damaged fallopian tubes, male factor infertility, ovulation disorders, premature ovarian failure, uterine fibroids, genetic disorders, and unexplained infertility.

1.2. Stages of the IVF Process

Step 1: Hormonal Stimulation

The first step of IVF is controlled ovarian hyperstimulation. The most common treatment is with a long GnRH-Agonist (Lupron) protocol where the gonadotropin hormones are suppressed in order to prevent premature ovulation. Once optimal suppression is achieved, the next step is the recruitment of multiple follicles by daily injections of gonadotropins. Ultrasound imaging and hormone assessments are used to monitor follicular development. When the follicles have reached the appropriate size, the final maturation of eggs is done with HCG administration. Egg retrieval is scheduled 34-36 hours after HCG injection.

Step 2: Egg Retrieval

Egg retrieval is performed under intravenous sedation. Ovarian follicles are aspirated using a needle guided by trans-vaginal ultrasonography. Follicular fluids are scanned to locate all available eggs. The eggs are placed in a special media and cultured in an incubator.

Step 3: Fertilization and Embryo Culture

If sperm parameters are normal, approximately 50,000 to 100,000 motile sperm are transferred to the dish containing the eggs. This is called standard insemination. Fertilization is assessed 16-18 hours after insemination. The fertilized eggs or zygotes are assessed on the second and third day after retrieval. If sufficient numbers of embryos exhibit good growth and development, they may be selected to

grow to the blastocyst stage. A day 3 embryo transfer is recommended for cycles with low numbers and/or poor quality.

Step 4: Embryo Quality

A grading system is used to assess the quality of the embryos.

Step 5: Embryo Transfer

Embryos are transferred on day 3 when they are at the cleavage stage (6-8 cells) or on day 5 when they have reached the blastocyst stage. Embryo transfer is a simple procedure that does not require any anesthesia. Embryos are loaded in a soft catheter and are placed in the uterine cavity through the cervix.

2. SEARCH CRITERIA METHODS

A follow-up systematic review was conducted on PubMED (MEDLINE) (2005-2017). Retrieved articles were reviewed for content and their references were used to identify other relevant articles. All abstracts were reviewed for the following key words: smoking, stress, caffeine, alcohol, obesity, nutrition, recreational drugs, BMI, exercise, lifestyle habits, in vitro fertilization, IVF, assisted reproductive technologies, and ART. The endpoints consisted of oocyte aspiration, fertilization, embryo transfer, implantation, achievement of a pregnancy, live birth delivery, and perinatal outcomes (e.g. birthweight, gestational age, multiple gestations).

Criteria for inclusion consisted of human studies, retrospective and case-control studies, prospective studies, and meta-analysis with detailed methods and statistical analysis sections. General exclusion criteria consisted of case reports, meeting abstracts, expert opinions, newspaper articles, magazines, and comments, all of which had insufficient information or no details on the lifestyle habit and/or IVF endpoints. Frozen embryos and oocyte donation studies were omitted because of the inability to determine the effect of lifestyle habits on IVF outcomes.

All of the studies evaluated and approved for this manuscript were based on specific criteria adapted from Sackett et al.[5] The criteria consisted of: (i) an appropriate study design, (ii) description of the selection and characteristics of subjects and comparison group with a sample size of .25, (iii) the existence of standardized IVF outcome measures, (iv) the use of standardized instruments and/or laboratory samples to verify lifestyle habits, and (v) the existence of multivariate analysis. For each lifestyle habit, all studies were compared and contrasted using these five criteria.[5]

Two independent reviewers selected and reviewed the publications to be included in accordance with the above-mentioned criteria. If there was discordance, a discussion resolved the issue, leading to a uniform decision. The final association between a lifestyle habit and IVF was based on the Institute of Medicine criteria (i.e. evidence sufficient, evidence suggestive but insufficient, evidence inadequate, and evidence suggestive of no association).[6]

3. RESULTS

3.1. Smoking

Tobacco smoking is the most prevalent lifestyle habit in society.[7] It is also described as the foremost reproductive poison of the 20th century.[8]

In the past decade, female smoking has been implicated in affecting every endpoint of IVF (Figure 1). One study reported that active smoking decreased ovarian response to hyperstimulation (i.e., 12.12 ± 5 versus 8.62 ± 4 mature oocytes retrieved) compared with nonsmokers.[9] A second study found that women who smoked required more hormonal stimulation during IVF, with decreased success.[8] Serum AMH

concentrations were lower among smokers resulting in no predictive value for ovarian response.[9] Furthermore, cigarette smoke increased the zona pellucida thickness of oocytes, thereby decreasing the quality of the eggs.[10] Female recent smoking caused a significant age-adjusted association between increased follicular fluid cotinine levels and a decreased number of ova retrieved.[11] Women who smoked also had both significantly lower quality and number of embryos compared to non-smoking patients.[10]

The relationship between smoking and failed pregnancies was striking as evidenced in four studies.[9, 12-14] There was a significant difference in pregnancy and implantation rates among mainstream and sidestream smokers when compared with nonsmokers.[12] Next, compared with nonsmokers, active smoking women had lower clinical pregnancy rates (29.6 versus 10.0%).[9] Compelling evidence was also provided in a systematic review and meta-analysis of 17 studies for a significant negative effect of cigarette smoking on IVF outcomes.[13] Specifically, smoking patients demonstrated significantly lower odds of clinical pregnancy per cycle (OR 0.56, 95% CI 0.43-0.73), significantly higher odds of spontaneous miscarriage (OR 2.65, 95% CI 1.33-5.30) and significantly higher odds of ectopic pregnancy (OR 15.69, 95% CI 2.87-85.76).[13] Pregnancy rates in non-heavy smokers (0–10 cigarettes/day) was significantly higher than in heavy smokers (>10 cigarettes/day) (52.2 versus 34.1%, respectively).[14] Interestingly, multiple pregnancies were significantly higher in heavy smokers (60 versus 31%).[14]

Recent female smoking was associated with significantly decreased live birth rates even after adjusting for age, cotinine concentration in follicular fluid, BMI, number of alcoholic drinks per week, and number of cups of coffee drunk per week.[11]

A meta-analysis reported that smoking patients had over two times the odds of live births per cycle (OR-0.54, 95% CI: 0.30-0.99).[13] The impact of smoking on the live birth rate in IVF treatment is comparable with an increase in female age of >10 years from age 20 to 30 years.[15]

In contrast to this body of literature, only one study found that smoking status did not significantly affect pregnancy outcome, live birth rate or any other indicated outcome,[16] while a second study did not reach statistical significance for smoking effects on pregnancy, livebirths, and miscarriages.[17]

The effects of sidestream (secondhand) smoke in women was also striking. In one study, using adjusted models, the researchers found a significant increase in the risk of implantation failure among women exposed to sidestream smoke compared with those unexposed [odds ratio (OR): 1.52; 95% confidence interval (CI):1.20 –1.92; risk ratio (RR) = 1.17; 95% CI: 1.10 –1.25].[18] They also found a significant decrease in the odds for a live birth among sidestream smoke-exposed women (OR= 0.75; 95% CI: 0.57 –0.99; RR= 0.81; 95% CI: 0.66 –0.99).[18] This study demonstrated that the effects of sidestream smoking are equally as damaging as mainstream smoke on fertility.[18]

In males, one study found no effects of smoking on IVF outcomes,[19] and another study reported decreased live births.[11] There were no studies that evaluated the effects of secondhand smoke in males on any of the IVF outcomes. Cigarette smoking among men did not have a significant negative effect on outcomes of IVF whether their partners were smokers or nonsmokers.[19]

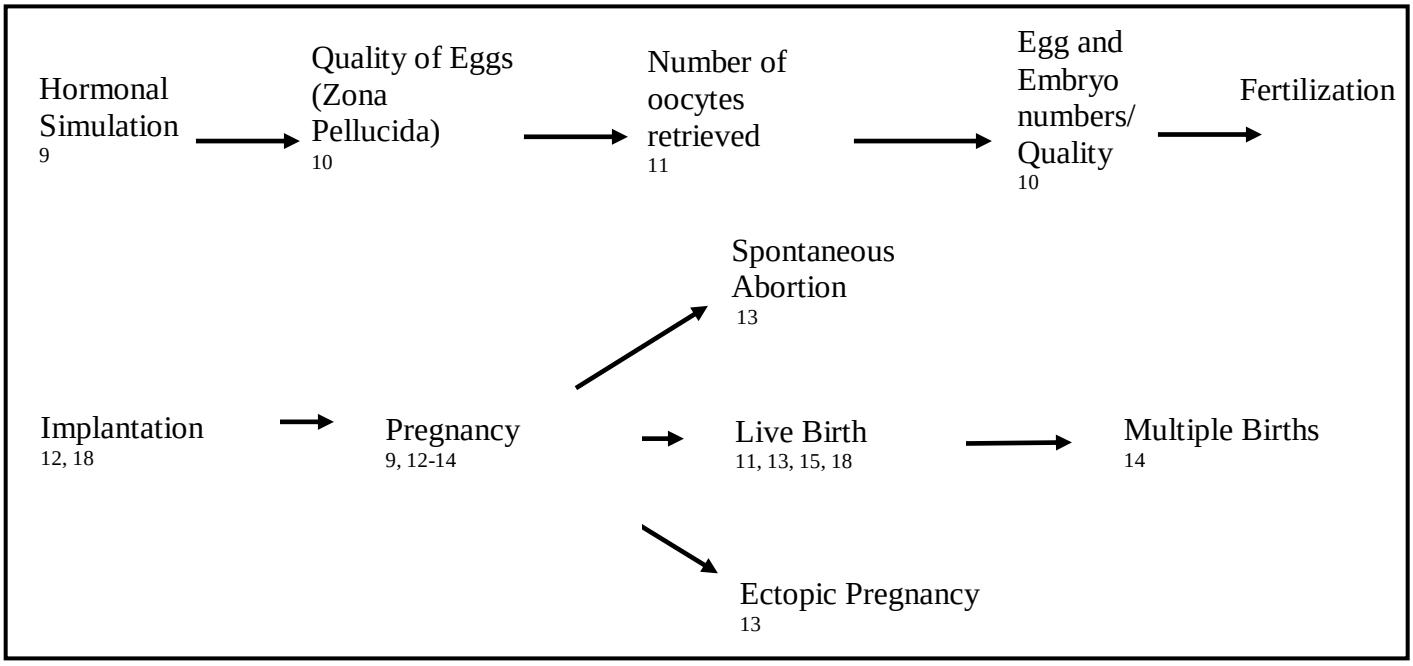

Figure 1: Effects of Smoking on IVF

3.2. Alcohol

One-half of all reproductive aged females report drinking alcohol.[20] Additionally, 1 in 10 pregnant women in the United States ages 18 to 44 years report drinking alcohol in the past 30 days.[21] In contrast, 58% of adult men report drinking alcohol in the last 30 days, while approximately 23% of adult men report binge drinking 5 times a month, averaging 8 drinks per binge.[22]

It is well known that alcohol use during pregnancy is linked to birth defects. However, there is a scarcity of research on the effects of alcohol on IVF outcomes. There are currently a total of four studies which investigated this area (Figure 2), and alcohol was quantified differently in each study: during the year, month, or week before IVF (for males and females),[23] pre-treatment alcohol intake,[24] daily drinking,[25] and at least four drinks per week by women and couples.[26]

In a 2014 systematic review on alcohol consumption and IVF, 389 studies were retrieved, two of which were considered eligible.[27] A total of 2,908 couples were analyzed in terms of pregnancy outcomes depending on drinking habits.[27] The first study of the systematic review reported that female alcohol consumption was associated with 2.86 times the risk of not achieving a pregnancy while male alcohol consumption increased the risk of not achieving a live birth by 2.28-8.32 depending on the time and type of alcohol.[23] The second study stated that the difference in odds ratios (OR) of live birth rates in women who drank at least four drinks per week compared with women who drank fewer was 0.84.[27] Paternal alcohol use levels 1 month, 1 week, and during the attempts were also associated with worse reproductive effects.[23]

A second study reported that daily drinkers experienced lower cumulative incidence of live births after the first three cycles, which may be clinically significant.[25] Daily drinkers were also at twofold increased risk of spontaneous abortion after the first cycle compared to non-drinkers.[25] In contrast,

Vittrup did not observe significant associations between male or female alcohol consumption and odds of live birth after assisted reproductive treatment.[28]

Women drinking at least four drinks per week had 16% less odds of a live birth rate compared with those who drank fewer than four drinks per week.[26] For couples in which both partners drank at least four drinks per week, the odds of live birth were 21% lower.[26] Hence, consumption of as few as four alcoholic drinks per week were associated with a decrease in IVF live birth rates.[26]

Finally, the adjusted percentage of initiated cycles resulting in live birth (95% CI) for women in increasing categories of pre-treatment alcohol intake was 34% (20, 52%) for non-consumers, 46% (36, 57%) for 0.1–6 g/day, 41% (29, 53%) for 6.1–12 g/day, 42% (31, 55%) for 12.1–24 g/day, and 41% (22, 63%) for >24 g/day (P, trend = 0.87), indicating that alcohol did not affect cycle initiation.[24]

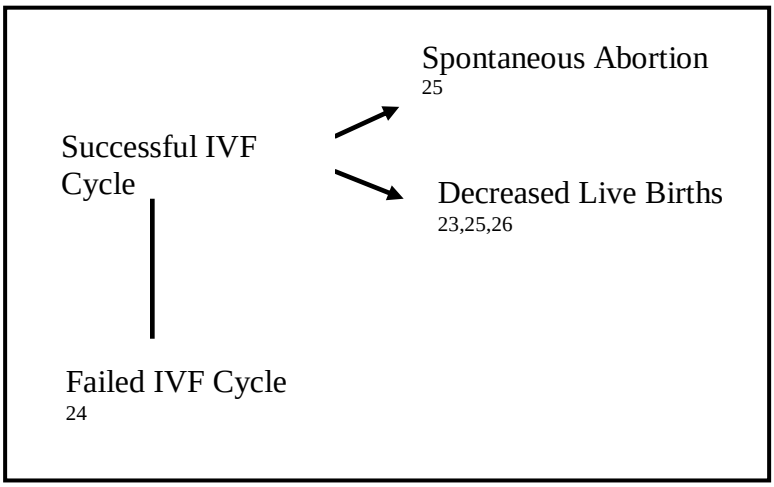

Figure 2: Effects of Alcohol on IVF

3.3. Exercise

As the health benefits of exercise are increasingly recognized, more women and men are participating in regular exercise. The Centers for Disease Control and Prevention recommends 30 minutes or more of moderate-intensity physical activity on preferably all days of the week. Although exercise has many health benefits, there is conflicting evidence with regard to the effects of low and high impact exercise on the outcomes of IVF.[29]

A study examining 2,232 women undergoing in vitro fertilization (IVF) found that women who engaged in cardiovascular exercise for 4 hours or more per week for as little as one year prior to the treatment had a 40% decrease in live birth rate (OR .6; 95% CI .4-.8), as well as higher risks of cycle cancellation (OR 2.8; 95% CI 1.5-5.3), and implantation failure (OR 2.0; 95% CI 1.4-3.1).[29] The type of exercise (e.g., walking) had no effect whereas strenuous exercise had a marked negative impact on IVF success.[29] Regular exercise before in vitro fertilization may negatively affect outcomes. In contrast, physical activity positively affected implantation (Coef: 9.4; p = 0.009), increased the chance of pregnancy (OR: 1.83; p = 0.013) and tended to decrease the risk of miscarriage (OR: 0.30; p = 0.068).[30] In addition, an inverse correlation was found between physical activity and BMI.[30] (Figure 3). There were no studies on physical activity in men.

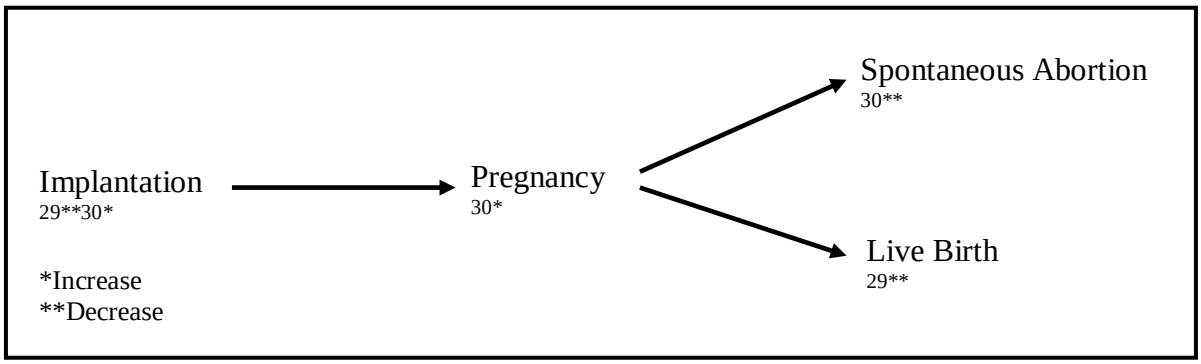

Figure 3: Effects of Exercise on IVF

3.4. Obesity

Obesity has become a worldwide epidemic, with approximately 1.9 billion adults being overweight and 600 million being obese as of 2014.[31] Moreover, obesity has negative effects on reproductive health. It has been established that obesity is associated with decreased natural fecundity, a decreased ovulation rate, increased time until conception, and increased rates of miscarriage.[32, 33] Additionally, an increased rate of pregnancy complications, including gestational hypertension, preeclampsia, gestational diabetes, postpartum hemorrhage, and fetal macrosomia, are all associated with obesity.[34,35]

Obesity also appears to have a significant impact on several IVF outcomes as evidenced by the following studies (Figure 4). Obese women had a significantly longer mean period of infertility ($P = 0.04$), and more anovulatory infertility ($P < 0.01$) compared to normal weight women.[36] In 487 couples initiating fertility treatment: (i) the number of cancelled cycles per woman was significantly higher in the obese group; and (ii) positive serum HCG decreased with increasing BMI. [36] Overweight and obese women had an increased risk of cancellation transfer and miscarriage rates, leading to poorer IVF outcomes.[37] Similarly in morbidly obese patients there was a significantly higher risk for IVF cycle cancellations.[38]

Obesity had a significant adverse effect on the mean embryo grade, the embryo utilization rate, number of embryos discarded, and cryopreserved.[39] Obesity also reduced the normal fertilization rate (coefficient [Coef.]: −16.0; $p = 0.01$).[30]

Furthermore, implantation, pregnancy, and live birth rates were poorer in obese women. In fact, pregnancy and live birth rates were reduced progressively with each unit of BMI (kilograms per square meter) with a significant odds ratio of 0.984 (95% confidence interval 0.972–0.997) and 0.981 (95% confidence interval 0.967–0.995), respectively.[40] In addition, the cumulative pregnancy rate after four IVF cycles was reduced as BMI increased.[40, 41]

A registry dataset spanning a 12-year period was analyzed for 706,360 treatment cycles when an embryo transfer was performed. In the group of obese women, the pregnancy rate decreased to 27%.[42]

In younger patients undergoing IVF, increasing BMI and advancing age resulted in a decreased pregnancy rate.[43] BMI has a significant negative impact on pregnancy, which diminished as patients reached age 35 years. After 36 years, BMI has a minimal impact on fertility.[43]

Increasing obesity was also associated with a significant rise in failure to achieve a clinical pregnancy with the use of autologous oocytes (P< 0.0001), but no difference was observed with donor oocytes.[44]

A recent systematic review of the effect of overweight and obese women on ART concluded that pregnancy rates in non-overweight women (20-25 kg/m2) are significantly higher (OR: 1.40; 95% CI: 1.22-1.60) than those in overweight women (>25 kg/m2).[45] Similarly, non-obese women (20-30 kg/m2) presented with significantly higher pregnancy rates (OR: 1.47; 95% CI: 1.20-1.80) than obese patients (>30 kg/m2).[45] Therefore, based on the current evidence, it can be concluded that obesity negatively affects IVF pregnancy rates.

In the recent systematic review of ten studies performed by Maheshwari et al;. the OR for miscarriage was significantly higher in overweight and obese women than in non-overweight and non-obese women, respectively.[45] A second study confirmed that obesity increased the risk of miscarriage (OR: 14.3; p = 0.03).[30]

Increased female and male BMI, both independently and combined, negatively influenced live birth rates after IVF treatments.[46] Among women using autologous oocytes who did conceive, failure to achieve a live birth increased with increasing obesity, more so among women <35 years of age.[44] Finally, obese and morbidly obese subjects had a significantly higher risk for obstetric complications.[38]

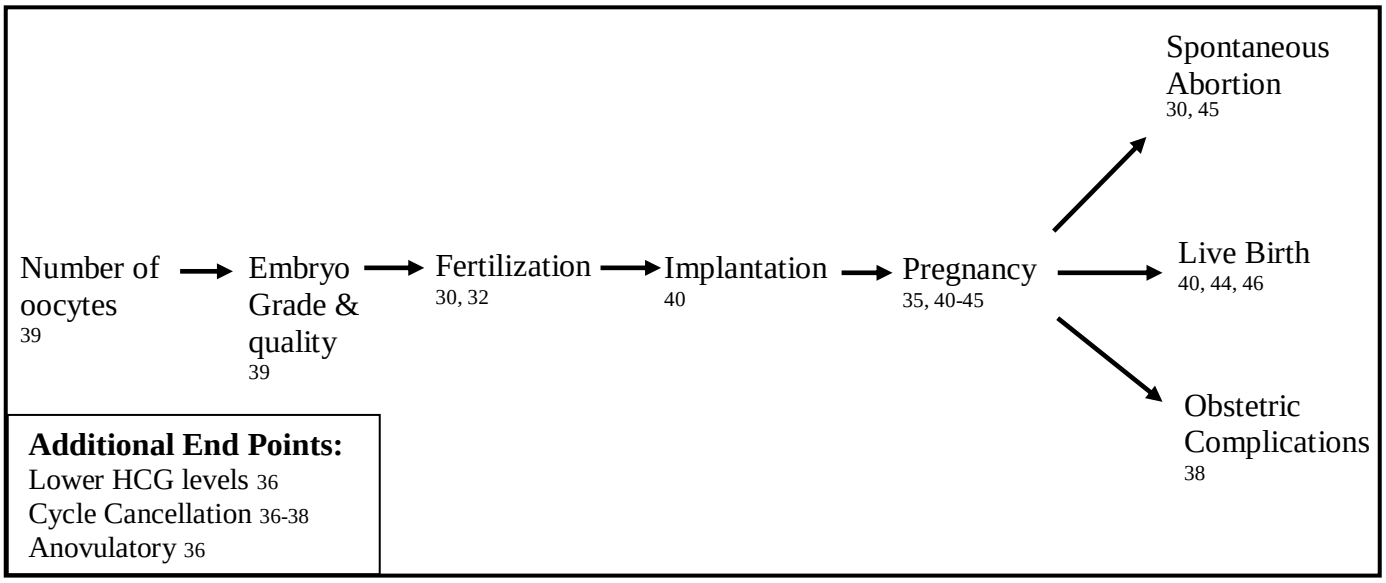

Figure 4: Effects of Obesity on IVF

3.5. Stress

In vitro fertilization (IVF) is psychologically and emotionally stressful.[47-48] Stress before, during, or after the IVF treatment is multidimensional.[47] There is the chronic source of stress caused by the threat of permanent infertility and loss of hope.[47] Another source of stress is the threat of the treatment itself, such as daily injections, blood draws, ultrasounds, oocyte retrieval, and the possibility of failure at any of the various phases.[47] The third source of stress is the risk of miscarriage.[47] Oocyte retrieval and pregnancy test proved to constitute the most stressful stages of the IVF cycle.[49,50]

The current literature on stress is still contradictory (Figure 5). Negative life events (which may indicate chronic stress)

negatively affected the number of oocytes harvested during oocyte retrieval.[51] In women with successful IVF treatments, lower concentrations of adrenaline at oocyte retrieval and lower adrenaline and noradrenaline at embryo transfer were detected compared to unsuccessful women.[52]

Non-pregnant women reported higher anxiety and depression scores during the pregnancy detection day compared with the pregnant group.[47] Furthermore, significant increases in serum norepinephrine and cortisol values were observed during ovarian stimulation. State Anxiety scores were negatively correlated with live birth rate and positively associated with serum norepinephrine and cortisol values. [47] In a final study, women who did not achieve a pregnancy while undergoing IVF experienced more negative life events than women who became pregnant.[53]

In contrast, Matthiesen et al. found no association between depression and clinical pregnancy.[54] Boivin et al. also concluded that pretreatment emotional distress is unlikely to be a cause of the failure of IVF.[55] According to Lintsen, neither baseline nor procedural anxiety, nor depression affected the ongoing pregnancy rates.[56]

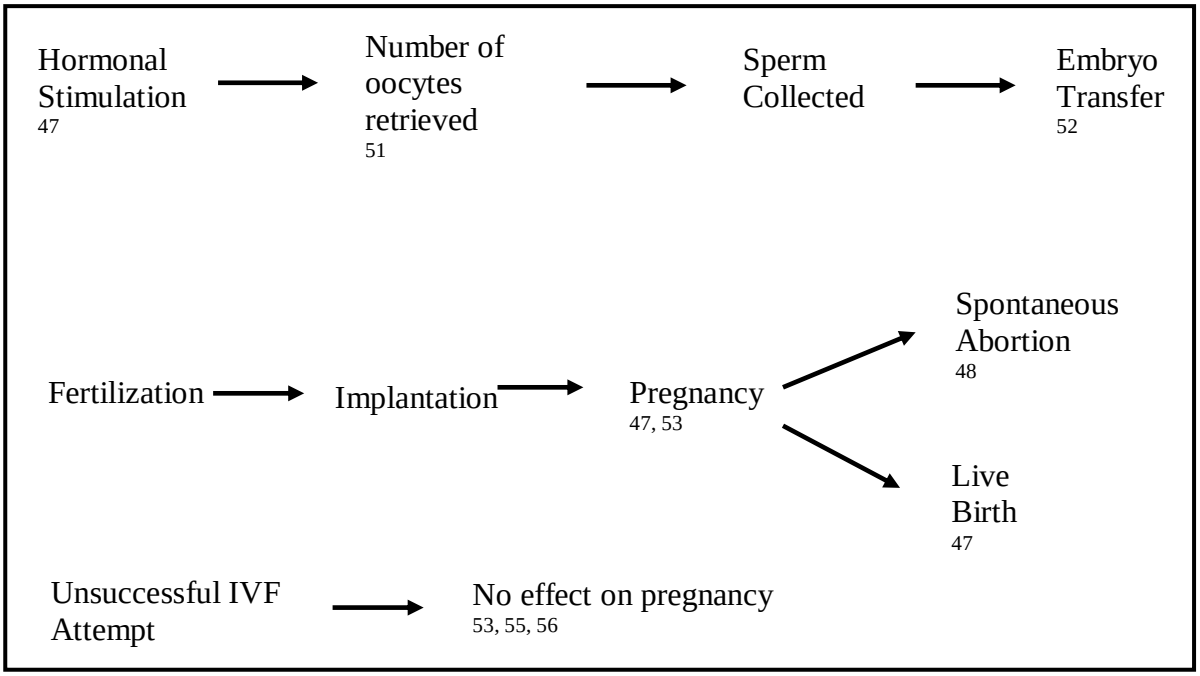

Figure 5: Effects of Stress on IVF

3.6. Recreational Drugs

Recreational drugs have many well-publicized side effects on mental, emotional, and physical health. It is well known that these drugs have profound effects on the brain, and cause addiction. However, what is often neglected is the negative impact these drugs can have on fertility.

Cannabis has widespread use and is often regarded as safe, particularly because of recent changes in legislation in the U.S., which may have reinforced this belief. However, marijuana can cause menstrual cycle dysfunction and lower sperm counts in men. The effects of marijuana and other recreational drugs on IVF are unknown.

A total of two publications in 2013[57] and 2014[7] reviewed recreational drugs on IVF. Both articles reported that evidence is weak due to an absence of studies because of ethical considerations and underreporting. To date, there are no studies on the effects of amphetamines/ecstasy, prescription opioids, cocaine, heroin, and anabolic steroids on IVF outcomes. There is only one study that suggests a negative impact of marijuana on IVF.[58] Klonoff-Cohen reported that the amount of lifetime heavy marijuana use adversely affected IVF/GIFT. [58] Women smoking more than 90 times in their lifetime had 27% fewer oocytes retrieved (P = .03) and 1 fewer embryo transferred (P < .05). Women smoking marijuana >10 times in their lifetime had infants 17% (P = .01) smaller at birth. If men smoked marijuana 11 to 90 times in their lifetime, there was a 15% decrease in infant birth weight (P = .03); if this increased to >90 times, there was a 23% decrease (P = .01). [58] Timing also played a role. Women smoking marijuana 1 year before IVF/GIFT had 25% fewer oocytes retrieved (P = .03), whereas couples had 28% (P = .04) fewer oocytes fertilized. Women and men who smoked in the past 15 years, had 12% (P = .04) and 16% (P = .03) smaller infants, respectively. [58]

3.7. Caffeine

The United States is the country with the highest amount of caffeine consumption (971 tons) followed by Brazil (969 tons).[59] A total of 85% of the U.S. population consumes at least one caffeinated beverage per day.[60] Coffee is the primary contributor to caffeine intakes in all age groups. Carbonated soft drinks and tea provide a greater percentage of caffeine in the younger (<18 years) age groups.[60] Caffeine consumption in pregnancy increases the risk of miscarriage and stillbirth, yet few studies have examined the effect of caffeine on IVF success.[61]

The impact of caffeine on IVF endpoints is as follows (Figure 6). One study determined that the number of eggs decreased as caffeine serum levels increased (P=0.011).[62] An increase in coffee consumption was positively associated with the number of aborted pregnancies (P=0.007), while the number of good embryos decreased with high tea consumption (P=0.015).[62] In contrast, greater caffeine intake by women was associated with a significantly lower peak estradiol level but not with the number of oocytes retrieved, fertilization rates, or implantation rates.[63]

There was no significant association between caffeine intake by men and live births, fertilization, or implantation.[63] In a separate study, there was a significant decline of sperm morphology by the additive impact of advanced age, high BMI, low sexual activity, and high coffee intake.[64]

Kesmodel, of Aarhus University Hospital in Denmark, analyzed information from nearly 4,000 women who underwent IVF at a large clinic.[65] The link between drinking more than five cups daily resulted in a reduced chance of pregnancy by 50% and live birth by 40%, even after the researchers adjusted for women's age, smoking habits, body mass index, and the reason for infertility treatment.[65]

There is only one previous study by Klonoff-Cohen[50] that assessed the effects of female and male caffeine consumption on IVF outcomes. In total, 221 couples were interviewed about their caffeine consumption (i.e., coffee, soda, tea and chocolate) during different periods of time prior to initiation of the ART procedure.[50] In women, the relative risk of not achieving a live birth was 3.1 (95% CI: 1.1-9.7) and 3.9 (95% CI: 1.3-11.6) for regular intake of over 2-50 and 50 mg/day, respectively.[50] The decrease in live births was explained mainly by the significant increase in the miscarriage rate of 19.8 (95% CI:1.3-300.9) and 10.5

(95% CI: 0.9-125.3) in women who usually consumed over 2-50 and 50 mg of caffeine per day (during their lifetime).[50] However, the wide CI resulting from the small sample size of this study makes the association between caffeine and miscarriage somewhat unreliable. There was also a trend towards lower infant gestational age among women who consumed over 50 mg/day of caffeine during the week of the initial visit.[50] In men who increased their usual intake by an extra 100 mg/day or consumed that quantity of caffeine during the week of the initial visit, the odds of having a multiple gestation increased by 2.2 (95% CI: 1.1-4.4) and 3.0 (95% CI: 1.2-7.4), respectively.[50]

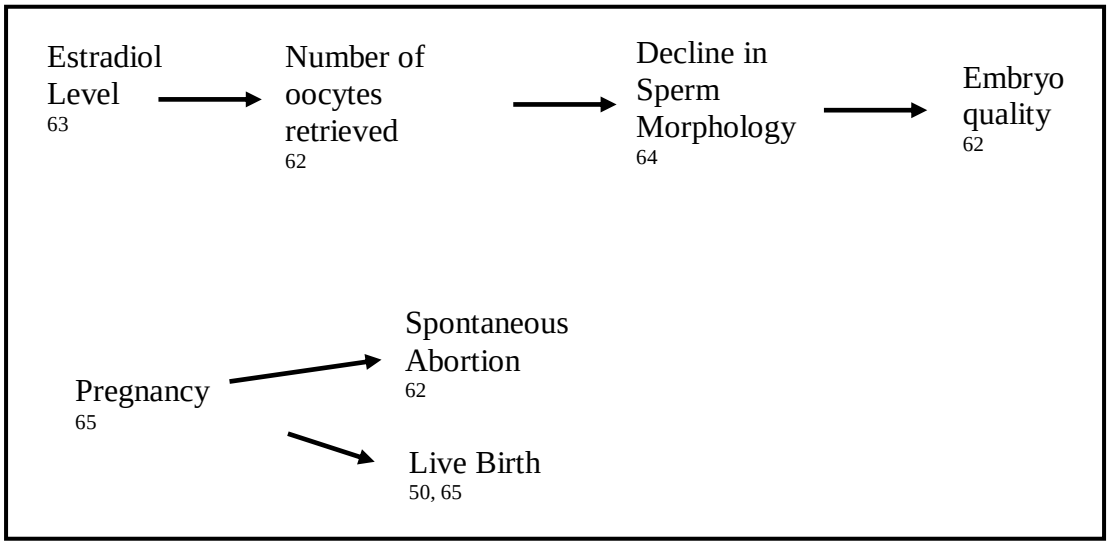

Figure 6: Effects of Caffeine on IVF

4. DISCUSSION

There is strong evidence that smoking affects almost every endpoint of IVF. From the span of 2005 until Sept. 2017, it has been determined that female smoking negatively affects hormonal stimulation,[9] oocyte quality[10] and number of eggs retrieved,[11] embryo quality,[10] and implantation.[12,18] Additionally, female smokers have lower pregnancy rates,[9,12,14] lower live birth rates,[11,13,15,18] higher spontaneous abortions,[13] more multiple births,[14] and ectopic pregnancies.[13] Cumulatively, this data supports the importance of discouraging cigarette smoking among female patients undergoing IVF.

Additionally, there is mounting evidence that obesity profoundly affects pregnancy (n=7 studies)[35, 40-45] and live birth rates[40,44,46] and is associated with cancelled cycles.[36-38]

The paucity of studies on recreational drugs leaves a vacuum in knowledge regarding their effects on IVF outcomes. Previous research from one study[58] reports that timing and amount of marijuana adversely affects IVF. Female lifetime marijuana (>90 times) resulted in fewer oocytes retrieved, whereas women and men who smoked in the past 15 years had smaller infants.[58] To date, there are no studies on the effects of amphetamines/ecstasy, prescription opioids, cocaine, heroin, and anabolic steroids on IVF outcomes. Hence, the evidence is inadequate regarding recreational drugs and IVF.

There are four studies on caffeine and IVF outcomes so the results are somewhat

limited. Caffeine decreased the number of oocytes,[62] affected embryo quality,[62] and increased the risk of miscarriages.[62] Additionally, drinking more than five cups of coffee daily significantly reduced chance of pregnancy by 50% and live births by 40%.[65] Finally, female coffee drinkers had over three times the risk of not achieving a live birth with IVF.[50] With the paucity of studies on caffeine and IVF, the evidence is inadequate to make any recommendations.

There is a growing body of literature on stress, which continues to be contradictory. Despite the possible negative impact of psychological variables on IVF outcome, the evidence remains inconclusive. The results were almost equally divided between four studies that found a negative effect of stress on number of oocytes,[51] embryo transfer,[52] and pregnancy,[47, 53] and three studies that reported no effect on IVF.[53, 55, 56] These contrasting results may reflect limitations in small sample size and study design (e.g., retrospective or cross-sectional) along with unstandardized choices of psychological instruments which are usually limited to a single stress parameter. The value of stress tests is controversial because women selecting IVF may have different personality characteristics than other women of reproductive age. Hence, there is no consensus regarding the ideal measure of stress for infertile women undergoing IVF. Moreover, the majority of related studies have reported clinical pregnancy as the key end point, without pursuing spontaneous abortion, premature delivery, multiple births, live births or other outcomes. Future studies about psychological stress and IVF should measure plasma and follicular levels of stress hormones, such as prolactin and cortisol to clarify the role of these hormonal mechanisms, and determine the neuroendocrine and physiological pathways that mediate effects on IVF outcomes.

The evidence for an association between alcohol and IVF is inadequate and unknown at this time due to the paucity of published articles. However, the three studies[23, 25, 26] all found a connection between female alcohol consumption and decreased live births.

The exercise literature is unexpected. One study speculates that exercise is beneficial[30] while the other study provides data that long-term exercise is dangerous.[29] The type, intensity, frequency, and duration of exercise is important to quantify in both men and women. Problems with self-reporting (under or over-reporting) and type of exercise could affect the validity of the outcome.

The quandary about the effects of lifestyle habits should have been resolved by this time. A previous summary in 2005 provided the basis for smoking, caffeine, stress, and alcohol.[50] Yet, over a decade later, there are still insufficient studies in these areas of caffeine consumption, alcohol consumption and illicit drug use and evidence is still equivocal.

The methodology for studying the implication of lifestyle factors on IVF outcome needs to be vastly improved. A thorough evaluation of the most important IVF outcomes, such as healthy live birth rates and neonatal characteristics, is essential. Moreover, studies should consider lifetime versus procedural timing of a lifestyle habit, as well as its type, quantity, frequency, duration and periods of abstinence. Future studies should include a comparison group, and study the contribution of male lifestyle habits as well as jointly (couples). Studies should adjust for potential confounders (e.g., patient characteristics such as age), as well as procedural factors (e.g., type of ovarian stimulation procedure). Lifestyle habits should be captured using a longitudinal design with multiple time points and adequate sample sizes, and diverse racial/ethnic groups. Self-report of lifestyle habits should be combined with biologic markers. Metabolites should be analyzed

throughout the entire IVF procedure (e.g., at initial clinic visit, during embryo transfer and after pregnancy outcome) in order to obtain more reliable conclusions. Additionally, other co-existing lifestyle habits should be evaluated because compounding effects of lifestyle habits are difficult to separate and this may result in a cumulative outcome. On the other hand, habits, which might be crucial for the outcome alone, may be obliterated by a multifactorial lifestyle influence.[6] Finally, researchers should identify underlying mechanisms attributable to each lifestyle habit and endpoint of IVF.

A national or international database could effectively and accurately capture lifestyle habits over time on thousands of couples undergoing IVF and evaluate the biggest contributors to an unsuccessful IVF attempt thereby helping to create guidelines for clinicians. Regardless, from a medical standpoint it is probably advisable for men and women contemplating IVF to be encouraged to engage in healthy lifestyles.

A structured educational program, ongoing wellness support, and therapeutic interventions (e.g., smoking cessation, relaxation techniques, substance abuse counseling) could be part of the comprehensive care received at fertility clinics in order to promote healthy lifestyle changes. With respect to smoking, nicotine patches and counseling could be prescribed prior to beginning a cycle of IVF. Healthcare professionals could promote alcohol and recreational drug abstinence. PCPs and reproductive endocrinologists could endorse monitoring weight and preventing obesity. Review of low impact physical activity and sensible exercise regimens could be discussed with reproductive endocrinologists and obstetricians. These healthy behavioral changes could facilitate optimal health in couples attempting to become pregnant with IVF, thereby improving their chances of successfully achieving a healthy live birth.

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