## **Original Article**

# Effects of exposure to cigarette smoke on the ovarian response to ovarian stimulation in infertile couples referred to the Isfahan Reproductive Fertility Center during 2007-2008

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## Abstract

**BACKGROUND:** The first step and a necessary prerequisite for a successful treatment of infertility is an adequate ovarian response to ovarian stimulation and it is a major challenge for both patients and health system. Therefore, it is very important to determine the factors related to ovarian response failure. One of the peripheral factors considered in the recent studies on infertility, is exposure to cigarette smoke. This study compares the ovarian responses to ovarian stimulation in infertile couples exposed and not exposed to cigarette smoke.

**METHODS:** It is a retrospective cohort study on 144 infertile women referred to the Isfahan Reproductive Fertility Center in 2007. Data were collected using a questionnaire, patient's medical files, tape measure and scale. Content validity and test re-test were used for validity and reliability and chi square and T test used for data analysis. Data were analyzed by SPSS software.

**RESULTS:** Findings showed that exposure to cigarette smoke increases poor response to ovulation induction (p = 0.001) in women under assisted reproduction treatment. However, it doesn't increase the number of injections necessary for ovarian stimulation.

**CONCLUSION:** Based on the results of this study, volunteers for the assisted reproduction techniques should be educated about the harmful effects of exposure to cigarette smoke on fertility. Also, there should be plans to increase the public awareness about the harmful effects of cigarette especially on fertility.

**KEY WORDS:** Exposure to cigarette smoke, ovulation induction, ovarian response failure.

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In most societies, motherhood role is the most important role for an adult woman.<sup>1</sup> Reproduction stabilizes the women's status in the society, family.<sup>2</sup> and contrary. Infertility in women causes a sense of incompetency in performing motherhood role and leads to their concern for the lack of family stability. According to the studies, about 50-80 million people around the world experience some kind of infertility in their life.<sup>3</sup> Various organic factors including female and male factors are associated with infertility. In addition to the organic factors, peripheral factors are also known to have negative effects on reproduction. One of the important peripheral factors that has negative effects on fertility is smoking which is also a threat to health.<sup>4</sup> Evidences have shown that smokers has less fertility.<sup>5</sup> Studies showed that smokers who are under treatment by assisted reproduction techniques (ART) has less success in fertility.<sup>6</sup> Although there are evidences for the negative effects of smoking on ovarian ability, the effects of exposure to the cigarette smoke has not been known yet. Studies reported that each

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one cigarette produces about 500cc smoke. It means that smoking 2 cigarettes produces one liter of smoke in the air and this smoke includes more than 4000 chemical poisons.7 Almost 75% of cigarette smoke enters the air and just 25% is inhaled by the smoker. And even half of this 25% will be transferred to that air by the smoker. So, people around the smoker are exposed to 85 to 90% of cigarette smoke and inhale it.8 Exposure to smoke increases nicotine, cadmium and aromatic hydrocarbons and affects the synthesis and metabolism of estrogen.9 It is probable that the increase of blood thickness of final products of cigarette smoke negatively affects the physiology of reproduction in those who are exposed to the cigarette smoke, which means negative effects on the fertility results.<sup>10</sup> Therefore, studies are focused on the primary and major factors of fertility to explain this relation. Edward et al showed that exposure to cigarette smoke had negative impacts on ovule maturity and affected the folliculogenesisand steroidogenesis inside the follicle.<sup>11</sup> Write et al found no significant difference between peak serum estradiol and number of ovules.<sup>12</sup> Also, studies have shown that nicotine, cadmium and poly-aromatic hydrocarbons which exist in the cigarette smoke have an antiestrogen effect and lead to decrease of ovarian reserve.13 An adequate ovarian response to ovarian stimulation is the first step, a prerequisite for successful treatment of infertility and a major challenge for both patients and health system. It is also very important to determine the factors related to ovarian response failure. In cases that the ovarian response to ovarian stimulation fails, physicians will often use more invasive treatments, which are significantly more expensive and have a higher risk (overly stimulation of the ovarian). This study aims to determine the ovarian response failure in infertile couples exposed to the cigarette smoke in comparison with those who were not exposed. Also, the mean number of necessary injections for adequate ovarian stimulation was compared between the two groups of infertile couples exposed and not-exposed to cigarette smoke referred to the Isfahan Reproductive Fertility Center.

#### **Methods**

This is a retrospective case-control cohort study carried out in one stage with two groups. The sample size included 144 infertile women (72 exposed to cigarette smoke and 72 not-exposed) referred to the Isfahan Reproductive Fertility Center for treatment in 2007 and wanted to use assisted reproduction techniques of in vitro fertilization (IVF), intrauterine induction (IUI), IC-SI and were under ovarian stimulation of HMG, FSH and had the entry criteria. Sampling was via simple method.

Inclusion criteria included age of 40 years old or less, willing to participate in the study, use of HMG and FSH for ovarian stimulation, Iranian nationality. Following cases were excluded from the study: patients who used clomiphene for ovarian stimulation, smokers (cigarettes or water pipe), drug or alcohol use, patients with one ovary, those with known ovarian endometrioma or diagnosed systemic endocrine diseases such as diabetes, Addison's disease, Cushing's syndrome, hypo-parathyroid, thyroid function disorders, patients who had a history of radiotherapy or chemotherapy, drinking more than 3 cups of coffee per day, patients who took medicine other than those of assisted reproduction treatment such as phenothiazines, anti-depressants, metoclopramide, butyrophenones, reserpine, amphetamine, methyldopa, cyclophosphamide, those with known systematic diseases such as chronic renal failure, liver failure, galactosemia, ovarian mumps infection and inflammation, known endometriosis, those who received ovule from others, those who rented their uterus or used donated fetus. Participants, who didn't want to continue or stopped their treatments for reasons other than ovarian response failure and ovarian hyperstimulation, were excluded from the study too.

Data were collected using questionnaire, patients' medical records and measurements. Collected data included height, weight and completed questionnaire. The questionnaire consisted of three parts. First part was questions on exposure; second part was demographic data and the cause of infertility; and the third part

included questions about the results of ovarian stimulation. The researcher introduced herself to the patients who were under ultrasound in her presence and studied the results of ultrasound. Based on the ultrasound results if the prescription time of HCG was known or ART was stopped due to ovarian response failure, the patient was interviewed about exposure to cigarette smoke. If the patient was exposed to at least smoke of one cigarette per day in a room with closed door during her past two menstruation cycle, she was placed in the exposed group. If the patient had no exposure to cigarette smoke or was exposed to at most one cigarette smoke in one month accidentally, she was placed in the not-exposed group. After this stage, those patients who had the inclusion criteria signed for the participation in the study and completed the questionnaire by interview, medical records and measurement of their height and weight. It should be mentioned that sampling was done at the time of last ultrasound or at the time of HCG prescription and the BMI was calculated via dividing. For validity of data, content validity was used and for reliability of the questionnaire test re-test was used. The correlation coefficient of questions was approved by 0.85 and higher. Since ultrasound was carried out accidentally, the distribution of participants in the two groups for undergoing ultrasound by doctors in the medical center was equal. Besides, the same scale was used to measure height and weight of all participants and in the beginning of each day the scale was checked and controlled by using a 5 kg weight. Data were analyzed using descriptive statistics and SPSS software.

### Results

There was no significant difference between the two groups of exposed and not-exposed to cigarette smoke, in age, frequency of doing ART, education, career, cause of infertility, economical situation, BMI and previous usage of OCP/ GnRH-agonist, but these results were expected according to the sample method.

The results of Chi square test (p = 0.001) showed a significant difference between the

frequency of poor response to ovarian stimulation in the two groups of exposed and notexposed to the cigarette smoke and there was 33.3% failure in the exposed group compared with 12.5% failure in the not-exposed group. The findings showed that most of women exposed to the cigarette smoke (47.2%) compared with 1.43% of not-exposed women used 15-30 injections for ovarian stimulation. The mean of injections in exposed group was 19.9 ampoules (SD = 9.7) and in not-exposed group was 19.8 ampoules (SD = 12.7) and independent t test showed no significant difference between the two group (p = 0.97).

### Discussion

The results of this study show that exposure to cigarette smoke increases poor response to ovarian stimulation in women under treatment with assisted reproduction techniques. Nemer et al study showed a significant difference between the two groups in poor response to ovarian stimulation.<sup>14</sup> Also, the study of Paszkowski et al showed a significant difference between the two groups in poor response to ovarian stimulation.<sup>15</sup> Vanvoorhis et al also reported a significant difference between the two groups in poor response to ovarian stimulation.16 In review of many studies on this topic, the researcher didn't find any study that have a different result and disapprove these results. The results of all studies agree with the findings of this study that there is a significant relation between exposure to cigarette smoke and poor response to ovarian stimulation. Then it can be concluded that exposure to cigarette smoke can lead to follicle discharge and can reduce the reproduction system function due to chemicals it contains. Cigarette smoke has toxic effects on ovary and its nicotine and metabolite can harm the granulose lute in cells. These alkaloids bond with the nucleus and cytoplasm protein and can potentially affect the follicle maturity and the ovule growth. However the results of our study showed no significant difference between the mean of ampoules used for ovarian stimulation in the two groups. Shiloh et al study on the impact of cigarette smoking on zona pellucida

thickness of oocytes and embryo prior to transfer into the uterine, cavity also showed no significant difference between the numbers of ampules in the two groups.<sup>9</sup> Miceli et al study had the same results too.<sup>17</sup>

Moreover, the results of Paszkowski et al study on the impact of tobacco smoking on the intra-follicular markers of oxidative stress revealed no significant difference in the number of ampoules used by women exposed and notexposed to the cigarette smoke.<sup>15</sup> Motejlek et al study also reported the same results.<sup>18</sup> But Nemer et al showed a significant relation between the number of ampoules and exposure to cigarette smoke and women who were exposed to tobacco smoke used more ampoules.<sup>14</sup> The disagreement of these results with the present study may be related to the matching of interfering factors such as BMI in the present study, because Motejlek et al study didn't match the groups. Besides, in the present study, prescription of ampoule changed based on the ovarian response and was not the same during the treatment. This condition can affect the results and needs further research.

Considering the effects of exposure to cigarette smoke on poor response to ovarian stimulation it is recommended to educate women who are volunteer to use assisted reproduction techniques in this regard and the health centers and clinics involved in treatment of infertility should consider increasing the public information about the harmful effects of cigarette smoke especially on fertility.

The researchers declare that have no conflict of interest in this study and they have surveyed under the research ethics.

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