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Research Article

The Relationship between Successful IVF and the Man's BMI and Smoking Habits in Couples with Unexplained Infertility- a Retrospective Study

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Keywords

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- Obesity
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Abstract

Background: Male adiposity has in previous studies, been reported to be connected with low levels of androgens and SHBG and high levels of estrogens. In men, high levels of estrogens can result in low levels of gonadotropins and testosterone and in turn these hormonal changes have been shown to be associated with a reduced semen quality. With the increasing prevalence of obesity in society today more knowledge is needed about how an increasing BMI, Body Mass Index (=kg/m^2) affect men's reproduction and fertility. One clinical observation is that more men who come for fertility treatment are overweighed or fat. As concerns the effect of smoking on male fertility, different studies have found diverse results. The hypothesis for this study was that male overweight and obesity would be associated with decreased success after Assisted Reproductive Treatment, ART. The hypothesis was the same for tobacco use among the men.

Aim: To evaluate if elevated body mass index among men influences the outcome of *in vitro* fertilization when it comes to live birth rate. To evaluate smoking and snuffing as confounders in men and their influence on live birth rate after *in vitro* fertilization.

Methods: 664 heterosexual couples with unexplained infertility, who had been accepted for ART, were included in a retrospective study of 1270 IVF/ICSI cycles during the years 2005-2013.

Results: Mean body mass index for the 664 men was 25.8 (range 18.1- 41.9). High male body mass index was negatively associated with live birth rate after ART with odds ratios in the different BMI-groups, <20, 20-24.9, 25-29.9 and >30 (odds ratios: 1.77, p-value=0.52, [0.32-9.92], odds ratio 1.0, vs. 0.99, p-value=0.97, [0.71-1.38] vs. 0.68, p-value=0.18, [0.39-1.19] respectively), although not statistically significant proved. Multivariable logistic regression showed that the likelihood of life birth rate after ART was increased if the male was a snuffer (odds ratio: 1. 46 p-value=0.042, [1. 0-2. 1]).

Conclusions: In this study, male body mass index did have negative influence on live birth rate after IVF/ICSI, although not statistically, probably due to a small sample of fat men studied (64 persons). When looking at odds ratio for live birth rate, in obese men, it was lower than in normal weighed men. Snuffers had statistically significant higher live birth rate after assisted reproduction than non-snuffers in all BMI groups.

INTRODUCTION

It has been seen in a number of studies [1-5] that the man's BMI is inversely related to the concentration of androgens in the body and to SHBG-levels. A decrease in the level of SHBG results in a decreased concentration of free testosterone in the blood [6]. The concentration of inhibin B decreases with an increase in BMI but this change is not accompanied by a compensatory increase in FSH. However, it has been shown that an increase in BMI in the man is positively related to estrogen levels. This relationship arises as a result of increasing conversion by aromatisation of androgens to estrogens in the peripheral fat tissue in overweight and obese individuals as compared with individuals of normal weight. High estrogen levels have a damaging effect on endogenous secretion of gonadotropin because they interfere with GnRH-pulsatility. Overweight men may, as a result, be affected by hormonal changes similar to those associated with hypogonadotropic hypogonadism, which is to say low gonadotropin- and testosterone concentrations. These hormonal changes that occur in overweight men are particularly evident in abdominal fatty tissue [7].

The concentration of adipokine leptin, the concentration of which is correlated with the mass of fatty tissue in obese men, inhibits the production of hCG-stimulated testosterone production by restricting the conversion of 17 OH-progesterone to testosterone. It appears that leptin has a direct effect on gametes when spermatocytes express the functional leptin receptors in a special stage of development. Leptin has accordingly specific receptors in the testicles [8]. The chronically elevated levels of leptin in the overweight and obese can lead to leptin resistance. This can in turn affect the level of GnRH in the hypothalamus and levels of LH and FSH in the hypophysis. This takes place through the so called KISS 1 neurons that are potent regulators of GnRH/LH/FSH- release. KISS 1 neurons express the leptin receptors and can therefore function as transmitters of metabolic information to the GnRH-neurons. In this way the KISS 1 system can function as a link between metabolic function and fertility [9-11].

The serum concentration of reproductive hormones has been shown to be related to sperm quality. A significant correlation has also been observed between the serum levels of inhibin B, LH, FSH and sperm parameters [5]. Studies differ concerning the exact mechanism by which BMI influences sperm quality. A meta-analysis of 21 studies covering a population of 13,077 individuals found that the risk of oligospermia and a zoospermia increased progressively with increased body weight with a two-fold higher prevalence among those with massive obesity compared with those with normal BMI [12]. According to some studies an increase in BMI results in a decrease in sperm concentration [2,3,12] and a lower motility of the sperm [12]. Yet according to other studies the men's BMI is not related to motility and morphology of the sperm [3,4]. According to one study [4] men's BMI does not affect sperm concentration. It has been observed that both sperm concentration and morphology affect the time that it takes for a couple to become pregnant; a decreased concentration and proportion of morphologically normal sperm resulted in an increase in the length of time to pregnancy [13].

Much has been published on the relationship between female fertility and overweight/obesity with the general conclusion being that female obesity has reproductive consequences in the form if irregular menstrual cycles, anovulation, increased risk of infertility, in increased risk of miscarriage in pregnant women [1,14,15]. It has also been observed that obese women respond less well to assisted fertilisation compared with women of normal weight. Studies have shown that obese women require a longer and higher-level stimulation with gonadotropins during IVF-treatment, that they have fewer eggs of lower quality after stimulation, that the frequency of pregnancy is lower among obese women following IVF compared with women of normal weigh, and that obese women have a greater risk of miscarriage in pregnancies resulting from IVF-treatment [1,16-19].

Atthe fertility unit in Linköping women with BMI >30 are not accepted as candidates for assisted fertilisation. Therefore we do not believe that BMI of the women in our study can have any decisive effect on the result as these women are few.

There are studies showing that overweight and obesity affect sperm quality [2,3,12] and it is therefore probably that men with high BMI and abnormal sperm test results will have a lower frequency of clinical pregnancy after treatment than will men of normal weight. It has even been observed that the incidence of obesity is higher among men with an infertility factor than among men with known such factors [2]. In our study only couples with unexplained fertility were included and that means men with normal sperm-test results according to the WHO definition which is: volume 2-5 ml, 40 million sperm in total, 15 million sperm/ml and sperm motility>40 %. Men with abnormal sperm tests were not included.

There are several studies examining how men's BMI affects the outcomes of assisted fertilisation [20-23]. These studies have, however, included men with known infertility factors as well as men without known infertility factors. This difference distinguishes our study from previous studies in as much as we have studied couples diagnosed as unknown infertility.

As concerns the effect of smoking on male fertility, different studies have found diverse results. In one study no direct association between smoking and sperm quality (morphology, concentration, and motility) [24]. In a study from Vine MF [25] a weak association was found between smoking and sperm quality but the relationship was stronger among healthy men (voluntary spermdonors) than among men who had been studied at an infertility clinic. In the same study no decrease in fertility had been found in smokers as a group but it was noted that since smoking had previously been associated with changes in sperm parameters smoking might affect fertility among those who already had diminished sperm quality. In a Swedish study from 2008 it was seen that smokers had a lower number of sperm than non-smokers, and the sperm concentration was 37 % higher among non-smokers than among smokers [26]. Snuff or smokeless tobacco for oral use, is available in many countries of the world. The products are of very different kinds, with the only common characteristic: to deliver nicotine to the blood stream via the oral mucosa. Today's Swedish moist snuff is made up of non-fermented, heat-treated finely ground tobacco with the addition of alkalizing salt and flavoring. The level of nicotine in the snuff pouch varies between 4 and 15 mg nicotine per portion, with 8mg of nicotine per portion as the most common. How much of this nicotine is absorbed by the body depends on how long you have one portion inside, so a comparison with eg cigarettes is very difficult to make. The uptake of nicotine in the blood is a little slower than during smoking but is more extended [27].

The effect of snuff use on male fertility is a research area that has as yet been little investigated. A probable reason for this is that it is almost only in the Nordic countries that men use snuff. The percentage of male snuff users in age group 16-84 in Sweden in 2012 was 21.2 % (±1.6 %) [28].

The hypotheses for this study were that the higher the BMI among men the lower the frequency of live births after IVF/ICSI compared with normal-weight men and that snuff users and smokers respectively have a lower frequency of live births after IVF/ICSI than non-smokers and those who do not use snuff.

The aim of this retrospective study was: to investigate if overweight and obesity in men affect the outcomes of IVF- och ICSI-treatment in a study population that excluded men with deviant sperm-test results. This was to determine if there were more relationships between overweight/obesity and infertility among men than simply deviant sperm-test results.

An additional aim was to study male snuff-users and smokers results on pregnancies of IVF och ICSI.

MATERIAL AND METHODS

All of the heterosexual couples included in the study had come to the Reproductive Medicine Center, RMC, in Linköping, Sweden between 2005 and 2013 because of infertility or involuntary childlessness during a period longer than one year. The study is retrospective and the data recorded in Fert Soft "Linne´Filer", a database for assisted reproductive treatment, have been analysed. Information on all patients who have sought help at RMC on the basis of infertility is recorded in this system as is all information on couples who have gone through IVF and ICSI treatment. The women and men leave information on weight and height and in the case of uncertainty are weighed and measured at RMC. The reasons for infertility such as ovarian and tubal factors, male factors, and unknown factors are recorded as well. The inclusion criteria used in selecting the couples that could participate in the study was IVF for unexplained infertility. The exclusion criteria were all other possible reasons for coming for treatment and/or that BMI-values were missing in the database for men.

At the start of the study, the records for all in the study group that had gone through treatment at RMC since 2005 (N =857) were examined. Of the 857, 16 couples had gone through Intra Uterine Insemination (IUI), 19 stimulations with clomiphene citrate and 137 couples had not gone through any kind of treatment. In total there were 172 couples that had either experienced treatment other than IVF/ICSI or had not been treated at all. BMI values were missing for 21 men who had gone through IVF- and/or ICSI-treatment with their partner. Thus 193 couples were excluded from the study, leaving 664 as our study population.

Studied factors were: BMI and age for men and women smoking and snuff use for men and women.

BMI was calculated as the weight in kilograms divide by the square of height in meters. Both the weight and height of the men and the women were obtained either by measurement at RMC or from self-reports. BMI-values were used to characterize the following categories: underweight <20 kg/m^2; normal weight: 20-24. 9 kg/m^2; overweight: 25-29. 9 kg/m^2; and obese: >30 kg/m^2.

Ethical considerations: The couples are given written information that the results after treatment would be sent to the Swedish national quality registry, Q-IVF, and that if they do not want to be included in the register, they must actively state this wish. The result of the couples' treatment is reported to the register once a year and is presented for group, not for individuals.

The study was approved by: The Regional Ethical Review Board in Linköping, 2014/244-31.

Treatment: Before treatment was started, a basal study of infertility of each couple was made. The examination of the man always includes sperm testing and infection screening for hepatitis, HIV och syphilis. A general physical examination should also be made. If the first sperm test results are abnormal, then the man must leave another sperm sample. If there are any special concerns then hormonal and/or genetic evaluation may be given depending on how abnormal the sperm test results are [29].

If the couple does not have any demonstrable infertility factors, then after two years of infertility they are offered treatment with IVF.

Hormonal stimulation: The woman is treated with Follicle-Stimulating Hormone, FSH, to stimulate the ovaries so that more follicles will grow and more eggs will mature. The hormonal stimulation is carried out following either short or long protocols. FSH or a combination of FSH/LH is injected once per day during a period of 10 to 12 days. The dose, growth, and treatment time are individual and cannot be determined in advance.

When three or more follicles are measured over 18 mm, the hCG injection for final maturation of the oocytes is planned. Thirty six to forty hours after hCG is injected the oocytes are retrieved with the help of vaginal ultrasound transducer in local anaesthesia.

The man leaves a sperm sample on the same day that egg extraction takes place. Using this sample, an analysis is made of the number of sperm and of their mobility. By using sperm preparation, sperm can be separated from the seminal plasma, which can adversely affect the egg and the intrauterine conditions. The sample is then diluted with nutrient liquid and is kept in heated storage until it is brought in contact with the eggs.

Intra-Cytoplastic Sperme Injection, ICSI, is used when the sperm sample displays less desirable parameters for the number of sperm and/or mobility. Fewer than one million mobile sperm present after sperm preparation is seen as an indication that ICSI is called for. The method requires that the sperm are drawn up into a thin glass pipette. This pipette is then inserted into the oocyte's cytoplasma by simultaneously holding the oocyte in place.

In more than 80 % of the treatments only one embryo is returned to the uterus but two embryos can be returned if the quality is diminished or if the couples have gone through more than three IVF treatments with no children born. In Sweden, no more than two embryos are ever emplaced.

Embryo emplacement is done with the help of a thin plastic catheter with the embryo inside; the catheter is put in the through cervix, guided by ultrasound. Once inside, the embryo is carefully expelled. Progesterone in the luteal phase also given as vaginal pills given three times per day for three weeks after egg extraction to that the uterus' mucous membrane will become receptive to the embryo.

If several embryos are of good quality after being cultivated, then those not used for implantation are frozen if the couple gives permission. The frozen embryos may be kept in storage for at most five years [29].

Statistical analysis: Statistical analysis was done to study outcomes concerning live births following IVF and ICSI treatment of couples with unexplained infertility. The relationship between demographic data and the type of IVF-treatment of patients was established with the chi-2 test.

In addition, logistic regression was carried out in order to determine if there were any confounding effects that for the man were related to BMI, smoking and snuff and age. For the women same confounders were chosen; smoking and snuff use, BMI and age any or all of which might have influenced the probability of live-births after IVF and ICSI.

The relationship between the frequency of live births after IVF and ICSI and the man's BMI was calculated with the Odds Ratio (OR) and with the 95 % Confidence Interval (CI). Significance was set at p-value= 0.05.

RESULTS

A total of 664 men took part in the study; the mean value of BMI for this group was 25.8 (18.1-41.9). The mean age of the men was 35.1 years (23-55) and of the women 32.8 years (24-43). The men were divided on the basis of BMI into four groups: Low weight, BMI <20, N=6 (0.9%), Normal weight, BMI 20-24.9, (43. 8%), N=291 Overweight, BMI 25-29.9, N=303 (45.7 %) and Obese, BMI >30, N=64 (9.6 %) (Figure 1). A total of 1270 IVF/ICSI treatments were carried out; for the distribution of these treatments (Figure 2).

An examination of the distribution of treatment in relation to the men's BMI shows that obese men were treated with ICSI to a greater extent than normal-weight and overweight men (Table 1). The percentage of obese men going through ICSI was 22.6 compared with 18.3 % and 18.2 % for normal weight and overweight respectively.

Live births

The total number of live births was 423 of which 278 were the product of fresh IVF (65.7 %), 77 frozen IVF (18.2 %), 55 after fresh ICSI (13.0 %) and 13 after frozen ICSI (3.1 %).

62% of the couples underwent only one fresh IVF or ICSI, 17% two fresh IVF or ICSI, three or more treatment only 3.2%. 16.4 % had used frozen embryos once, 9.2% twice and 0.33% three times or more. The routine in most IVF clinics in Sweden is that frozen embryos are used before a new fresh IVF treatment is offered.

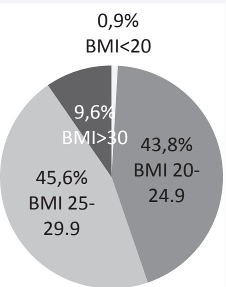

Figure 1 BMI distribution in men (n= 664).

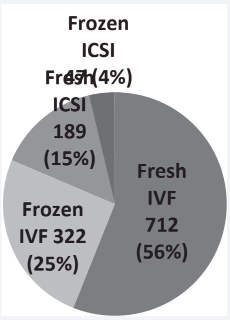

Figure 2 Distribution of 1270 IVF treatments.

Table 1: IVF or ICSI treatment depending on man's BMI Men with BMI < 20 were not counted because of too few persons n=6.

		BMI men	
Treatment	20-24,9	25-29,9	>30
IVF	469 (81.7%)	467 (81.8%)	86 (77.5%)
ICSI	105 (18.3%)	104 (18.2%)	25 (22.6%)

No more than 58 men (8.7 %) were smokers, 170 (25.7%) used snuff (Figure 3). Snuffers had an OR of 1.46 of having children after IVF (significant) compared to non-snuffers/non-smokers. Men with BMI> 30 were more frequent snuffers, Figure 4. Smokers had an OR of 0.92 of having children, p-value 0.73 (Table 2), compared to non-smokers/non snuffers.

It is evident that the older the woman, the lower the probability of giving birth after treatment (OR=0.93, p-value=0.004. The age of the man did not affect the probability of giving birth after IVF/ICSI, OR=0.95 and p-value=0.338 (Table 2).

The time between the registration of the couple at the fertility clinic and the time they started treatment influenced the probability of having a live birth. The longer the time interval before treatment, that is to say a long period of infertility, the lower the probability of having a child, OR=0, 77and p-value=0,000 (Table 2).

BMI in women did not affect the results of the men neither did smoking (n=40). Among women 63% were of normal weight and only 1.5 % of the women had BMI over 30.

Of the total group of normal weight men 63.6% had children after IVF and in all 185 children were born. In the group of overweight men 64.7% had in all 196 born children. In the group of obese men 37 children were born. 57. 8% of obese men had a child after IVF. The odds ratio decreased with increasing BMI; the OR of the underweight group was 1.77 (p-value=0.517), overweight 0.99 (p-value=0.966), and obese 0.68 (p-value=0.176), compared to normal weight men (Table 2). None of the results were statistically significant.

DISCUSSION

The likelihood of having a child after fresh IVF is about 30 % per treatment and with frozen embryos about 20 % per treatment in general [30]. It is at times difficult to compare results between different countries in view of the fact that different routines are followed concerning how many embryos are emplaced during a treatment. But in our study where at most two embryos were restored, the chance per treatment of having a child, taking into account that both fresh and frozen embryos were used, was 33.2% for the total population. One reason for our being able to get better results than were obtained in the ESHRE study [30] is probably due to our having chosen to only study couples without known infertility factors. We have also excluded couples that had a diminished chance for having a child.

The chance to have children after fresh IVF is about 30% per treatment and about 20% of freezing reversed embryo per treatment [30]. It can sometimes be difficult to compare results

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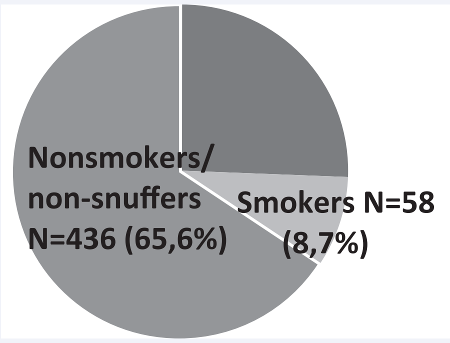

Figure 3 Distribution of non-smokers, non-snuffers, smokers and snuff users n= 664.

Table 2: Probability of having a child divided in BMI groups in men, age and tobacco users. Logistic regression, significant p-value ≤ 0. 05.

Live Births	Odds ratio	P-value	[95 % conf. Interval]
BMI men			
20-24,9	1,00		
25-29,9	0,99	0,966	0,71-1,38
>30	0,68	0,176	0,39-1,19
<20	1,80	0,517	0,32-9,92
Smoking man	0,92	0,762	0,53-1,60
Snuff man	1,46	0,042	1,01-2,09
Age man	0,95	0,338	0,95-1,02
Age woman	0,93	0,004	0,88-0,98
No tobacco in men	1,00		

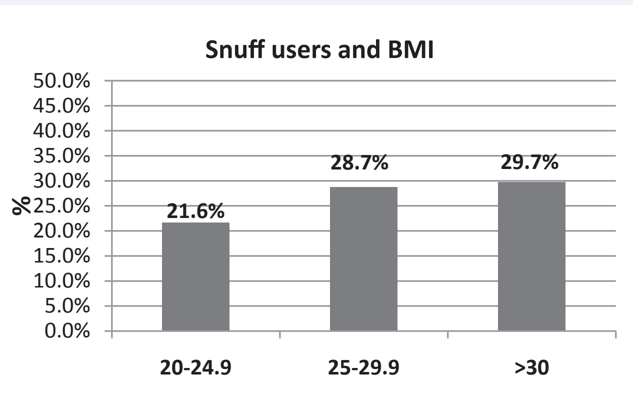

Figure 4 Distribution of snuff users in BMI groups. Men with BMI < 20 were excluded because of too few persons n=6.

across countries, since they have different routine on how many embryos to transfer per treatment. In this Swedish retrospective study no more than maximum two embryos were transferred, the chance to have children per treatment; in terms of both fresh and freezing of embryos was 33.2% of the total study population.

The odds ratio decreased in relation to men's BMI as concerned live births, but this relationship was not statistically significant. A possible explanation of this failure to reach significance is that the number of men in the group with BMI>30 (n=64) was too small.

As it is a retrospective study we could not count how many men with high BMI would be able to take part. No power calculations were made because of this. Now that we have the results we are able to determine the number needed for our hypothesis to be supported with statistically significant results.

It could be a weakness that both the men's and women's BMI were obtained from self-reporting. It has been shown that self-reported BMI-values may result in over estimation of as much as +0.19 kg for men and +0.17 kg for women [31]. Underestimation of BMI-values was observed only among women in the 55-64 year old age group in that study. Both men and women underestimated their weight and height, and this resulted in slightly higher BMI-values than the true values. In a study of Roberts RJ [32] self-reporting of weight and height resulted in an underestimation of the true prevalence of overweight and obesity in the study population of 4.5 % in the men and 6.7 % in the women. It is difficult to determine how self-reporting of weight has affected our study, but since weight is not taken into consideration for men who are to be part of the treatment program in the study any risk of conscious failure to report true values is reduced. Unintended incorrect reporting may have occurred, however, which results in a risk of bias.

BMI is a measure that places an individual's body weight in relation tothe individual's height. As a result, this measure does not directly reflect the percentage of body fat in an individual. It is therefore possible that some men in our study that were classified as overweight or obese had, in reality, a high percentage of muscle mass. This makes it possible that we have overestimated the percentage of overweight and obese men and instead should determine the percentage of body fat in the men. This is of importance when it has been seen that a transformation of andogeneous to ostrogeneous takes place in peripheral fat tissue through aromatisation. High ostrogene levels have a damaging effect on the endogenous gonadotropin secretion because the ostrogene interferes with GnRH-pulsatility. Overweight in men can therefore be affected by hormonal changes that resemble those hypogonadotropic hypogonadism. This does not, however, affect men with a large percentage of muscle mass who nevertheless are possibly classified as overweight or obese in our study [1-5].

A review of previous studies shows that the researchers investigated the relationship between the man's BMI and clinical pregnancy, live-births, and sperm quality among other things. In these studies it was observed that male overweight was associated with decreased chance of clinicalpregnancy after IVF but not after ICSI [13-16] and also with a reduced frequency of live births after IVF [23]. Another survey [22] showed that the extent of fertilisation after IVF was higher among obese men but BMI was not associated with clinical pregnancy and live births. What distinguishes these studies from our study is that within the study populations there were couples with various types of infertility factors, for example pathological sperm results.This can be one reason why previous studies found results that differ from our findings. High BMI may, according to some researchers, influence sperm quality in the form of a decrease in sperm, concentration [2,3,12] and lower mobility of the sperm [12]. The observation that both sperm concentration and sperm morphology influence the time it takes for a couple to become pregnant in studies of men with pathologic sperm test resultscould be explained as a result of overweight or obesity, even though this has not been reported or observed in these studies.In this survey we excluded couples with known infertility factors such as deviant sperm test results and it is possible that we thus excluded men with pathologic sperm test results on the basis of high BMI. This is yet another possible reason for our being unable to get statistically significant results as concerns the percentage of live births in relation to the man's BMI. One might also speculate that the consequences of overweight and obesity on clinical outcomes of IVF treatment were caused by sperm quality that in our study was normal in all of the men (volume 2-5 ml, 40 million sperm in total, 15 million sperm/ml and sperm motility>40 %) . If we had included men with deviant sperm-test results, we probably would have had a different result.

A possible explanation of the hypothesis that overweight and obese men would experience worse outcomes after treatment even though sperm-test results are normal is that there are still functions in sperm that cannot be measured, for example adipokine leptin's influence on the sperm.

The total number of snuff-using males in our study was 170, 25.7 % of the total number of men in the study. Surprisingly, we found a significantly higher probability of having children after IVF among snuff users whatever the man's weight was, and, the group of men with BMI> 30 had the highest percentage of snuff users, almost 30%. These results are contradictory since the probability of successful live births among the normal-weight group was greatest as indicated by the odds ratio. This raises the question whether snuff use could reduce the effects of high BMI among the men, but this is purely speculation at present. There are very few scientific data on snuff use and fertility, and the literature does not offer any reasonable biologic explanation for snuff users having greater success in producing babies after IVF than nonusers.

We found no relationship between smoking on the part of the men and the probability of successful outcomes resulting from IVF treatment. This result is not surprising given the findings from one study showing that smoking did not affect sperm quality [24] or another study that found that the association between sperm quality and smoking was weak and that no decrease in the fertility of smokers as a group had been found [25]. A Swedish study from 2008 showed that sperm concentration among smokers was 37 percent lower in smokers than in non-smokers [26]. These results differ from results from other studies, but since we excluded men with poor spermsthis probably excluded the possibility of determining possible negative results of smoking on fertility. This explains our finding that smoking did not affect the probability of live births following IVF.

In summary, we see a tendency for obese men with normal results from sperm tests to be less successful in producing children after IVF and ICSI but we have been unable to provide significant data in this regard.

The probable reason for our results is that the study sample is small and that we have excluded all couples with known infertility factors and thereby have excluded all men with pathologic results from sperm tests. In order to go further to determine if there is a significant relationship, new studies with a larger study population are needed to support our finding of a decreasing chance with increasing male BMI as concerns the success rate for live-births after IVF. If such proposed studies were to demonstrate a statistically significant relationship between male BMI and percentage of live births after assisted fertilisation, larger, prospective experimental studies would be needed.

The new data resulting from this study were used to demonstrate a statistically significant result concerning snuff users and the success rate after IVF compared with the success rate for those who do not use snuff. The reasons for and possible processes involved in leading to this positive effect are not known. More studies are needed to determine if our results hold for larger populations.

We want to make clear that we do not want to encourage infertile men to begin to use snuff on the basis of the results of this study for two reasons. First; is that it has been established that snuff use has adverse effects on health [27]. Second; our study is, to the best of our knowledge, the first to show that snuff users are more successful in having children as a result of IVF than are men who do not use snuff. Given the results from this study, we cannot recommend that men who come to the fertility clinic cease using snuff to improve their chance of having a child after treatment.

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