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The preconception diet is associated with the chance of ongoing pregnancy in women undergoing IVF/ICSI treatment

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BACKGROUND: Subfertility and poor nutrition are increasing problems in Western countries. Moreover, nutrition affects fertility in both women and men. In this study, we investigate the association between adherence to general dietary recommendations in couples undergoing IVF/ICSI treatment and the chance of ongoing pregnancy.

METHODS: Between October 2007 and October 2010, couples planning pregnancy visiting the outpatient clinic of the Department of Obstetrics and Gynaecology of the Erasmus Medical Centre in Rotterdam, the Netherlands were offered preconception counselling. Self-administered questionnaires on general characteristics and diet were completed and checked during the visit. Six questions, based on dietary recommendations of the Netherlands Nutrition Centre, covered the intake of six main food groups (fruits, vegetables, meat, fish, whole wheat products and fats). Using the questionnaire results, we calculated the Preconception Dietary Risk score (PDR), providing an estimate of nutritional habits. Dietary quality increases with an increasing PDR score. We define ongoing pregnancy as an intrauterine pregnancy with positive heart action confirmed by ultrasound. For this analysis we selected all couples ($n = 199$) who underwent a first IVF/ICSI treatment within 6 months after preconception counselling. We applied adjusted logistic regression analysis on the outcomes of interest using SPSS.

RESULTS: After adjustment for age of the woman, smoking of the woman, PDR of the partner, BMI of the couple and treatment indication we show an association between the PDR of the woman and the chance of ongoing pregnancy after IVF/ICSI treatment (odds ratio 1.65, confidence interval: 1.08–2.52; $P = 0.02$]. Thus, a one-point increase in the PDR score associates with a 65% increased chance of ongoing pregnancy.

CONCLUSIONS: Our results show that increasing adherence to Dutch dietary recommendations in women undergoing IVF/ICSI treatment increases the chance of ongoing pregnancy. These data warrant further confirmation in couples achieving a spontaneous pregnancy and in randomized controlled trials.

Key words: preconception counselling / nutrition / IVF/ICSI treatment

Introduction

The preconception diet is often inadequate in women planning pregnancy (de Weerd *et al.*, 2003). Nutrition and lifestyle factors, comprising diet, exercise, stress, alcohol- and drug use, smoking and obesity affect reproductive performance, also during assisted reproduction (Anderson *et al.*, 2010). Despite the available knowledge on the relation between poor nutrition and lifestyles and the risk of fertility problems, congenital malformations and maternal pregnancy complications (Chavarro *et al.*, 2007; Vujkovic *et al.*, 2007, 2009a,b, 2010; Gardiner *et al.*, 2008), there are few initiatives that aim to structurally offer preconception counselling on these topics in a clinical setting to couples planning pregnancy. Screening is the first step in counselling. Screening on lifestyle factors, such as smoking and obesity, is relatively straightforward, compared with that based on nutritional quality (Thompson and Subar, 2001; Román-Viñas et al., 2009). There are many different questionnaire tools to address nutrition, designed to measure diet and nutrient intake as accurately as possible. These tools differ in their mode of administration, elaborateness and validity (Thompson and Subar, 2001; Román-Viñas *et al*., 2009). However, most of these tools are not suitable for clinical practice, because of time and financial constraints. If we can screen nutritional behaviours using a simple clinically applicable questionnaire, however, this may be a first step in changing poor nutritional behaviours in order to ultimately contribute to the improvement of reproductive capacity and performance.

Studies performed on the relation between (micro)nutrients and fertility also provide evidence that nutrition affects fertility in both men and women (Wong *et al*., 2002; Gardiner *et al*., 2008). Indeed, the aim of nutrition and nutritional advice is to ensure an adequate intake and status of (micro)nutrients. Ensuring that an adequate nutrient status is attained through counselling is difficult and troubled by various factors such as nutrient interactions, ethnic variation in nutritional habits, day-to-day variation in intake, misreporting and the method of evaluation (Thompson and Subar, 2001; Román-Viñas *et al*., 2009). In addition, there is still much debate on what is the recommended daily intake for specific nutrients (Román-Viñas *et al*., 2009). At present, the Food Frequency Questionnaire is the most applied and appropriate tool to quantify and qualify nutritional habits.

Time and costs are major issues also in the development of preconception care. As a result, screening and counselling on nutrition in a clinical setting is a trade-off between validity and applicability. The obtained information and offered advices should be simple, understandable and applicable for the patient-couple, regardless of differences in demographics.

The Netherlands Nutrition Centre is the official government funded institution that undertakes public health initiatives to improve nutrition in the Dutch population (The Netherlands Nutrition Centre, 2009). Based on the general recommendations of the Netherlands Nutrition Centre for a healthy diet, which are developed to ensure a sufficient nutrient intake, we devised a questionnaire to estimate nutritional intake in subfertile patient-couples using six simple questions. In the current clinical study, using this simple questionnaire we addressed the influence of a healthy diet on the chance of ongoing pregnancy after IVF/ICSI treatment.

Materials and Methods

Between October 2007 and October 2010, patient-couples planning pregnancy, visiting the outpatient clinic of the Department of Obstetrics and Gynaecology of the Erasmus MC, University Medical Centre Rotterdam, the Netherlands were offered preconception counselling at the clinic 'Achieving a Healthy Pregnancy' (AHP). At the first gynaecological visit, couples were referred for preconception counselling on nutrition and lifestyle after having received a flyer with information and a self-administered questionnaire. The questionnaires were filled out at home and included six questions on nutrition. We extracted the following additional data from the questionnaires: age, ethnicity, educational level, indication for referral, lifestyle factors [smoking, alcohol, exercise levels (type of exercise, frequency and duration), stress (yes/no and cause of stress) and drug use], use of medication over the counter and vitamin supplement use. During the preconception counselling, the questionnaires were checked by the counsellor and discussed in detail with the patient-couple. Height and weight were measured to calculate the body mass index (BMI = weight in kilograms divided by squared height in meters). Within 3 weeks after counselling, the participating couples and the gynaecologist received a letter in which the identified (un)healthy lifestyle and nutritional factors and recommendations in detail were reported. Every patient-couple was invited for a follow-up visit to evaluate their compliance to the recommendations. In our population, 46.2% made use of this opportunity.

The six nutritional questions covered the intakes of the main food groups: whole wheat (including cereal consumption), unsaturated oils, vegetables, fruit, meat and fish. This was based on the dietary recommendations of the Netherlands Nutrition Centre. These questions provide an overall estimate of the nutrition of a person. The current guidelines are at least four slices of whole wheat bread daily (or comparable servings of cereals), the use of monounsaturated or polyunsaturated oils, $\geq$200 g of vegetables daily, $\geq$2 pieces of fruit daily, $\geq$3 servings of meat or meat replacers weekly and $\geq$1 servings of fish weekly. Based on these questions we calculated the Preconception Dietary Risk score (PDR). When the intake of each food group met the recommendations of the Netherlands Nutrition Centre, a score of one point was assigned. Thus, the maximum PDR score was six and represented highly adequate nutrition according to recommendations of the Netherlands Nutrition Centre.

Patient-couples who received their first IVF/ICSI treatment with embryo transfer within 6 months after AHP were selected for our analysis. The information on the IVF/ICSI treatment was extracted from the database of the Erasmus MC fertility clinic and included treatment protocol, number of retrieved oocytes and transferred embryos and treatment outcome. The primary outcome was ongoing pregnancy, defined as a pregnancy with positive fetal heart action at around 10 weeks after embryo transfer confirmed by ultrasonography.

Data analysis was carried out using SPSS 17.0 for Windows (SPSS Inc., Chicago, IL, USA). Continuous variables are reported as Median (interquartile range). Univariate statistical comparisons are done using the non-parametric Mann-Whitney-*U* test. Proportions are compared using the χ^2 statistic. To address the influence of nutrition on the primary outcome, we applied multivariable logistic regression with expression of the effect estimate in odds ratios (OR). We considered several confounders: age, BMI, treatment indication, smoking status, alcohol use, exercise levels, stress, ethnicity, education, number of transferred embryos and ovarian stimulation protocol. Because couples are offered a second visit to the AHP-consult, we also considered the change in the PDR, with those visiting just once receiving a conservative score of '0', reflecting no change. We applied a backward analysis, with the inclusion of higher order variables. During the backward process a variable was included into the analysis if its *P*-value of $<$0.10 and inclusion changed the effect estimate of the variable of interest $>$10% (Kleinbaum and Klein, 2002).

Results

Of the 1270 patient-couples participating in this study up to the date of analysis, 199 couples received their first IVF/ICSI treatment with embryo transfer within 6 months after AHP consultation. Women undergoing IVF/ICSI treatment were more often of Dutch origin and less often of non-European origin (60.8 versus 53.1% and 27.6 versus 37.1%; $P = 0.04$). In addition, treated women were more likely to consume alcoholic beverages (62.8 versus 48.6%; $P < 0.001$), which resulted from the different ethnicity distribution between the groups. Women undergoing IVF/ICSI treatment were older and the duration of subfertility longer than those who did not receive this treatment (33.6 versus 32.1; $P < 0.001$ and 28 versus 22; $P < 0.001$, respectively) and had a slightly lower BMI (23.8 versus 24.8; $P < 0.01$).

Of the 199 couples undergoing their first IVF/ICSI treatment, 35% became pregnant and 26% sustained an ongoing pregnancy, whereas in 62% no pregnancy could be achieved. For 3%, the outcome of treatment is unknown. Of the 199 couples, 92 made use of the opportunity to visit the AHP-consult a second time. In this group, those fallen pregnant were slightly overrepresented (56.9 versus 43.0%; $P = 0.09$).

Table I shows the characteristics of couples undergoing IVF/ICSI treatment stratified for pregnancy status. Women with an ongoing pregnancy tended to be younger (32.5 versus 33.6; $P = 0.06$). In addition, women and men with an ongoing pregnancy were more often non-smokers (9.8 versus 24.6%; $P = 0.03$ and 20.4 versus 36.5%;

Table I **Baseline characteristics for couples undergoing IVF/ICSI treatment, stratified for ongoing pregnancy ($n = 193$).**

	Ongoing pregnancy ($n = 51$)	No pregnancy ($n = 142$)	P
Women			
Age (years); median (IQR)	32.5 (30.2–35.3)	33.6 (29.7–38.7)	0.06
Ethnicity; *n* (%)			0.29
Dutch	34 (66.7)	83 (58.5)	
European	7 (13.7)	15 (10.6)	
Non-European	10 (19.6)	44 (31.0)	
Education level; *n* (%)			0.08
High	24 (50.0)	50 (37.6)	
Intermediate	19 (39.6)	57 (42.9)	
Low	5 (10.4)	26 (19.5)	
Subfertility; *n* (%)			0.84
Primary	31 (60.8)	84 (59.2)	
Secondary	20 (39.2)	58 (40.8)	
Reason of subfertility; *n* (%)			0.40
Male	56 (39.4)	22 (43.1)	
Female	39 (27.5)	8 (15.7)	
Combined	15 (10.6)	7 (13.7)	
E.c.i	32 (22.5)	14 (27.5)	
Duration of subfertility (months); median (IQR)	34 (17–44)	28 (18–45)	0.63
Smoking (yes); *n* (%)	5 (9.8)	34 (24.6)	0.03
Alcohol use (yes); *n* (%)	32 (62.7)	87 (61.3)	0.85
BMI (kg/m^2); median (IQR)	24.0 (21.8–29.2)	23.8 (21.8–27.2)	0.41
PDR; median (IQR)	3 (2–4)	3 (2–4)	0.28
Whole wheat (yes); *n* (%)	22 (43.1)	55 (38.7)	0.63
Fats (yes); *n* (%)	33 (64.7)	89 (62.7)	0.93
Vegetables (yes); *n* (%)	12 (23.5)	32 (22.5)	0.92
Fruits (yes); *n* (%)	12 (23.5)	22 (15.5)	0.21
Meats (yes); *n* (%)	47 (92.2)	128 (90.1)	0.87
Fish (yes); *n* (%)	29 (56.9)	68 (47.9)	0.31
Men			
Smoking (yes); *n* (%)	10 (20.4)	50 (36.5)	0.04
BMI (kg/m^2); median (IQR)	26.1 (24.4–27.8)	26.2 (24.0–28.9)	0.62
PDR; median (IQR)	3 (2–4)	3 (2–4)	0.83
Whole wheat (yes); *n* (%)	30 (58.8)	106 (74.6)	0.03
Fats (yes); *n* (%)	34 (66.7)	92 (64.8)	0.72
Vegetables (yes); *n* (%)	10 (19.6)	28 (19.7)	0.98
Fruits (yes); *n* (%)	8 (15.7)	22 (15.5)	0.94
Meats (yes); *n* (%)	48 (94.1)	133 (93.7)	0.65
Fish (yes); *n* (%)	28 (54.9)	70 (49.3)	0.44

BMI, body mass index; PDR, Preconception Dietary Risk score; IQR, interquartile range; E.c.i., unknown cause of subfertility.

$P = 0.04$). The proportion of adherence to the recommendations for the main food groups comprised in the PDR, i.e. what proportion of women scored a point for the PDR for each food group was comparable between those fallen pregnant and those that did not. Without adjusting for any confounders, both women with an ongoing pregnancy and those without pregnancy had a PDR score of 3 (Table I, $P = 0.28$).

However, the logistic regression analysis shows an association between the PDR of the woman and the probability of ongoing pregnancy after IVF/ICSI treatment [OR 1.65, confidence interval (CI): 1.08–2.52; $P = 0.02$] (Table II). Thus, a beneficial increase in the PDR with one point associates with an increase of 65% in the chance of ongoing pregnancy after the first IVF/ICSI treatment within 6 months after counselling. The OR is adjusted for the confounders: treatment indication, age of the woman (squared), BMI and smoking status of the woman and the PDR and BMI of the partner. Interestingly, an increasing PDR of the men seemed to reduce the chance of pregnancy after IVF/ICSI treatment. After including the interaction between treatment indication and PDR of the man, the association between PDR of the man and the chance of pregnancy was conditional on female factor infertility. Thus, the PDR of the man did not affect the chance of pregnancy after IVF/ICSI treatment. Factors such as alcohol use, exercise and stress levels, ethnicity, education level, ovarian stimulation protocol, smoking of the man, the change in the PDR at the second visit, duration of subfertility and indication for treatment did not show effects according to the pre-specified criteria (Kleinbaum and Klein, 2002).

Table II **Predictors for ongoing pregnancy.**

	β	Odds ratio	95% CI	*P*
Age^2 (woman)	−0.022	0.98	0.96–0.99	<0.01
BMI (woman)	0.078	1.1	0.99–1.19	0.10
BMI (man)	−0.064	0.94	0.85–1.04	0.23
Smoking (woman)	−0.99	0.37	0.12–1.11	0.08
PDR (woman)	0.50	1.65	1.08–2.52	0.02
PDR (man)	−0.054	0.95	0.48–1.86	0.88
Treatment Indication				0.26*
E.c.i	REF			
Male	−0.49	0.61	0.23–1.62	0.32
Female	−1.21	0.30	0.09–1.01	0.05
Combined	−0.19	0.83	0.48–1.86	0.78
Treatment indication by PDR (man)				0.21*
E.c.i	REF			
Male	−0.31	0.74	0.32–1.70	0.47
Female	−1.14	0.32	0.11–0.92	0.03
Combined	−0.42	0.66	0.22–1.97	0.45

BMI, body mass index; PDR, Preconception Dietary Risk score; E.c.i., unknown cause of subfertility.
**P*-value reflects the overall significance of Treatment Indication/Treatment Indication by PDR (man).

Discussion

In this study, we show that the quality of the preconception diet of patient-couples undergoing a first IVF/ICSI treatment associates with the chance of ongoing pregnancy after IVF/ICSI treatment within 6 months after preconception counselling tailored on nutrition and lifestyle. After adjusting for several covariates a beneficial one-point increase in the PDR reflects a 65% increased chance for ongoing pregnancy (Table II).

There are many different tools to measure nutrition (Thompson and Subar, 2001; Román-Viñas *et al.*, 2009). The goal of these tools is to estimate qualitative and quantitative nutrient intake through the diet mainly in a research setting (Román-Viñas *et al.*, 2009). Our simple clinically applicable tool is based on the recommendations of the Netherlands Nutrition Centre, which are developed to ensure sufficient nutrient intake (The Netherlands Nutrition Centre, 2009). This tool does not estimate quantitative or qualitative nutrient intake but in a binary fashion it addresses whether daily nutrient intake of six main food groups (fruits, vegetables, meat, fish, whole wheat products and fats) is sufficient. Although we were able to account for several potential confounders, it is important to realize the considerable variability in the reporting of day-to-day nutritional habits conditional on obesity, education level, perceived health and ethnicity (Thompson and Subar, 2001). Nevertheless, because we discussed the questionnaire in detail with the patient-couple during the consultation, we were able to address any ambiguity in the reporting of nutritional habits and asked for additional information if necessary.

Previously, Vujkovic *et al.* (2010) have investigated the association between adherence to the Mediterranean diet using the Food Frequency Questionnaire (FFQ), comprising 195 questions, and the chance of biochemical pregnancy after IVF/ICSI treatment. This diet comprised high intakes of vegetable oils, vegetables, fish, and legumes and low intakes of snacks. High adherence to the Mediterranean diet associates with a 40% increased chance of biochemical pregnancy on Day 15 after embryo transfer. Here, we show a comparable effect for the adherence to the recommendations of the Netherlands Nutrition Centre and the chance of ongoing pregnancy after IVF/ICSI treatment only using a lower resolution and clinically applicable questionnaire.

Studies mostly focus on the relation of (micro)nutrient status, or markers thereof, and reproductive outcomes (Cetin *et al.*, 2010). Given that (micro)nutrients are primarily derived from the diet it should be interesting to investigate through which specific (micro)nutrients the effect of nutrition is mediated. Here the effects of B vitamins, such as folic acid, on reproduction could help explain mechanism through which nutrition mediates its effects on reproduction. Indeed, various studies by Vujkovic *et al.* (2007, 2009a,b, 2010) show that certain dietary patterns are beneficial with regard to reproductive outcomes and associate with B vitamin concentrations. Nevertheless, despite this knowledge, there are few initiatives in reproductive medicine to translate these findings into clinical practice. Combined with a recent study from our group by Hammiche *et al.* (2011), we show that preconception counselling on nutrition seems effective, and now also results in an improved pregnancy chance after IVF/ICSI treatment.

During the AHP-consult we counsel patient-couples to adopt, if necessary, a healthier diet, stop smoking, alcohol and drug use, to increase their exercise levels and subsequently lose weight. Afterwards, couples are invited for a follow-up visit, to review their compliance. Possibly, not only the baseline difference in nutrition affects the chance of ongoing pregnancy after IVF/ICSI but also the improvement in nutrition. Of the couples that returned for a second AHP visit, there was a significant improvement of the PDR, but no significant difference in the change of the PDR between women getting pregnant and those who did not (data not shown). Including the change of the PDR, as measured during the second visit, in the final model did not influence the effect of the PDR, as measured during the first AHP visit, on the chance of ongoing pregnancy, suggesting that the effect of nutrition is mediated through baseline differences. The study by Hammiche *et al.* (2011) in the ongoing AHP-cohort in couples, who consulted the AHP twice, shows a beneficial increase in the PDR. This was most notably driven by an improvement in fruit (+15%) and fish intake (+13%). Additionally, self-reported exercise levels (+44%) and folic acid containing supplement use (+17%) improved, which are not included in the PDR. Although not significant in the study of Hammiche *et al.* (2011), self-reported use of vegetables, whole wheat products, vegetable oil and meat, comprised in the PDR, and the distribution of the BMI groups improved, with fewer obese people (−3%). These findings suggest a significant uptake of the counselling. Therefore, it would be interesting to address further in depth whether an increase in the PDR at a second visit associates with an increased chance of ongoing pregnancy after IVF/ICSI treatment.

Paternal dietary and lifestyle factors affect semen quality (Vujkovic *et al.*, 2009a; Pacey, 2010) and thereby could influence assisted reproduction treatment success. Here, we are not able to identify a significant influence of the PDR of the man on IVF/ICSI treatment outcome. Only in the case of female factor infertility, the PDR of the man appeared to influence the chance of pregnancy. Nevertheless, the unintuitive direction of this association likely reflects the more adequate nutritional habits of men in couples that did not fall pregnant as a result of female factor infertility as opposed to those that did fall pregnant (mean + 1 PDR point, data not shown). Female factor infertility is not influenced by the nutrition of the man. In addition, because our study consisted of IVF/ICSI cycles that resulted in a good quality embryo suitable for transfer, this suggests that the effect of maternal nutrition on IVF/ICSI treatment outcome is primarily mediated through its provision of adequate nutrients to the early transferred embryo.

In addition to various nutritional factors that affect the chance of pregnancy after IVF, lifestyle factors such as smoking and overweight status, together with exercise levels and stress could affect the chance of pregnancy after IVF/ICSI treatment (Fedorcsák *et al.*, 2004; Campagne, 2006; Morris *et al.*, 2006; Dechanet *et al.*, 2011). To our knowledge, the only study that specifically addresses the influence of physical exercise on IVF/ICSI treatment outcomes is by Morris *et al.* (2006). This study with a large sample size failed to find an association between current exercise levels and IVF/ICSI treatment outcomes, which is how this topic was addressed during the AHP-consult. Including this measurement of physical exercise in the analysis did not affect the influence of the PDR on the chance of ongoing pregnancy. During the consult we also obtained general information on stress, giving a crude estimate of stress. Here, we failed to show an effect of stress on the chance of pregnancy. Given the evidence in the literature for the relation between IVF/ICSI treatment success and physical exercise and stress, implementing more detailed measures for both features could help us to further detail the influence of nutrition using the PDR on effects of IVF/ICSI treatment. Although marginal and not significant, the BMI appears beneficially associated with the chance of ongoing pregnancy. This is in contrast with firmly established evidence, which shows a decline in IVF/ICSI treatment success with an increasing BMI (Fedorcsák *et al.*, 2004). As noted, we counselled couples to adopt a healthier lifestyle. Although it is not possible to show such an association in the sample for this analysis, possibly the largest improvement in dietary and lifestyle factors is noted in overweight/obese people who require and perceive the greatest necessity for change. Studies focussing on weight loss suggest that it is not necessary to obtain a healthy weight but weight reduction of 5–10% is already sufficient to improve fertility and endocrine parameters (Kiddy *et al.*, 1992; Clark *et al.*, 1995). Thus, considering the time lag between treatment and counselling, the discussed results from Hammiche *et al.* (2011), the fact that a slight weight reduction is often sufficient to improve the chance of pregnancy, and the notion that overweight people could perceive the greatest necessity to take up counselling, it might be possible that BMI measured prior to treatment is a correlate of dietary and lifestyle improvements and thereby explain the positive association between BMI and pregnancy chance in this study.

Conclusion

We show here that adherence to recommendations of the Netherlands Nutrition Centre associates with an increased chance of ongoing pregnancy after the first IVF/ICSI treatment. We addressed this topic using a low-resolution and clinically applicable questionnaire. In line with studies on weight reduction (Clark *et al.*, 1995; Palomba *et al.*, 2010), this study provides evidence that programmes aimed at beneficially changing preconception nutrition and lifestyle factors should be considered a first-choice treatment for unexplained subfertility. A next step for these investigations would be to address whether a beneficial change in nutrition associates with an increase in the chance of ongoing pregnancy after IVF/ICSI treatment.

Authors' roles

J.M.T. acquired, analysed and interpreted data, drafted the manuscript and designed study. M.E.C.B. acquired and analysed data and drafted manuscript. E.A.P.S. critically revised the manuscript for intellectual content. F.H. acquired data. W.G.I. acquired data. J.S.E.L. critically revised the manuscript for intellectual content and conducted data interpretation. R.P.M.S.T. drafting of manuscript, interpretation of data, critical revision of manuscript for intellectual content and study design.

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Conflict of interest

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