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ORIGINAL ARTICLE ***Reproductive epidemiology***

Pre-pregnancy maternal fasting plasma glucose levels in relation to time to pregnancy among the couples attempting first pregnancy

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STUDY QUESTION: What is the relationship between pre-pregnancy maternal glucose levels and fecundability in Chinese couples?

SUMMARY ANSWER: Elevated pre-pregnancy maternal glucose levels were associated with fecundability, as reflected by prolonged time to pregnancy (TTP) among the couples with no prior gravidity.

STUDY DESIGN, SIZE, DURATION: Based on the National Free Pre-conception Check-up Projects supported by the Chinese government, 2 226 048 eligible couples attempting first pregnancy and participating in the project from 2015 to 2016 were included. They were followed-up for 1 year or until they reported pregnancy.

PARTICIPANTS/MATERIALS, SETTINGS, METHODS: The Kaplan–Meier method was used to estimate the cumulative pregnancy rate in each menstrual cycle, and the discrete-time analogue of the Cox models was used to estimate the fecundability odds ratios (FORs) and 95% CIs by different pre-pregnancy maternal glucose levels (impaired fasting glucose (IFG) or diabetes as compared to normal).

MAIN RESULTS AND THE ROLE OF CHANCE: The cumulative pregnancy rate for 12 cycles of the normal fasting plasma glucose (FPG) level group was 42.29%, significantly higher than that of the IFG (35.52%) and diabetes groups (31.52%). After adjusting for confounding factors, the FORs were 0.82 (95% CI: 0.81–0.83) and 0.74 (95% CI: 0.72–0.76) for the IFG and diabetes groups, respectively, as compared to the normal group. The association between pre-pregnancy maternal FPG levels and the FORs was non-linear, and the optimal FPG level for greatest fecundability (shortest TTP) was 3.90–4.89 mmol/L.

LIMITATIONS, REASONS FOR CAUTION: The findings from this register-based cohort study require cautious interpretation given that information bias would be inevitable for single FPG measurements and for TTP calculations that were based on telephone follow-up information. Additionally, because couples who achieved pregnancy during their first menstrual cycle in the study were excluded, the pregnancy rates reported were low and possibly biased.

[†]These authors contributed equally and were considered co–first authors.

WIDER IMPLICATIONS OF THE FINDINGS: The current report suggests that elevated pre-pregnancy maternal glucose levels were associated with prolonged TTP. Early evaluation and preventive treatment for female partners with IFG or diabetes in a pre-pregnancy examination are necessary.

STUDY FUNDING/COMPETING INTEREST(S): Funding was provided by the National Key Research and Development Program of China (grants No. 2016YFC1000300 and 2016YFC1000307), the National Natural Science Foundation of China (grant No. 81872634), the CAMS Innovation Fund for Medical Sciences (grant No. 2018-I2M-1-004), the National Human Genetic Resources Sharing Service Platform (grant No. 2005DKA21300) and the National Population and Reproductive Health Science Data Center (grant No. 2005DKA32408), People's Republic of China. The authors have no conflicts of interest to declare.

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Key words: pre-pregnancy / diabetes / impaired fasting glucose / time to pregnancy / fecundability

Introduction

Infertility is a severe medical and social problem, which reflects a vital aspect of reproductive health and ultimately induces psychological distress (Lakatos *et al.*, 2017). In high-income countries, ~15% of the population is affected by infertility, while in low-income countries the percentage can be even higher (range 9–30%) (Petraglia *et al.*, 2013). With a population more than four times that of the US, the infertility problem in China has become global research focus. A recent study reported that the prevalence of infertility among Chinese women attempting pregnancy was 25% (Zhou *et al.*, 2018). In recent decades, more studies have focused on the evidential association between infertility and somatic health, especially diabetes (Eisenberg *et al.*, 2016; Whitworth *et al.*, 2011). The findings may have important implications regarding development of potential prevention strategies for infertile women with diabetes since blood glucose levels can be effectively controlled through regular exercise and healthy diet managements.

The economic burden associated with the epidemic of diagnosed or undiagnosed diabetes and prediabetes is increasing (Cefalu *et al.*, 2014). Wang *et al.* (2017) estimated that the prediabetes prevalence in China reached 35.7% in 2013, while merely 36.5% of diabetic patients were aware of their diagnosis. With the increasing incidence of diabetes among young adults (Zhang and Ning, 2014), we are confronted with immense concerns in health hazards associated with impaired glucose tolerance and impaired fasting glucose (IFG). Some studies have conveyed that diabetes mellitus, including type 1 and 2, are associated with infertility (Eisenberg *et al.*, 2016; Jonasson *et al.*, 2007; Whitworth *et al.*, 2011), but data from prospective studies are still limited, and the underlying mechanism is not fully resolved. To our knowledge, no studies have explored the relationship between IFG and fecundability.

Given the fact that couples with no prior gravidity are predominate among those who desire to have children, and the probability of achieving first pregnancies among these couples might not be impacted by previous pregnancy outcomes and assisted reproductive technology, we focused on these couples and used the data from the National Free Pre-conception Check-up Projects (NFPCP) to explore the relationship between pre-pregnancy maternal glucose levels and couples' time to pregnancy (TTP) (a widely used effective index to evaluate the fecundability accurately) (Joffe, 1997; Sundaram *et al.*, 2017) and, furthermore, to determine the optimal fasting plasma glucose (FPG) level for shortest TTP.

Materials and Methods

Study population

The NFPCP is a nationwide population-based cohort study project supported by the Chinese government, aiming to reduce the incidence of adverse pregnancy outcomes throughout the country. The project design, organization and implementation have been described previously (Liu *et al.*, 2017; Wang *et al.*, 2018a; Zhang *et al.*, 2015). A total of 3 507 490 Chinese couples who had no prior gravidity and whose female partners were between the ages of 20–49 participated in the NFPCP from 1 January 2015 to 31 December 2016 were enrolled in our cohort. According to the exclusion criteria, couples were excluded if they were not planning for pregnancy or if they had certain medical conditions that resulted in difficulties or risks in getting pregnant or if they female partner reported irregular menstrual cycles (details are given in Fig. 1). It is noteworthy that a few female partners who were pregnant in their first menstrual cycle in the NFPCP might not realize that they have been pregnant at the time of enrolment. In order to ensure that all female partners were not pregnant when they joined the project, we merely included the couples whose female partners had at least one normal menstrual cycle after participating in the NFPCP. Thus, a total of 2 226 048 couples were included in the analysis. This study was approved by the Institutional Research Review Board at the National Health Commission and the National Health Council's Ethics Review Committee.

Data collection and operational definitions

All couples completed a standardized family health questionnaire administered by experienced local health professionals at baseline. Data concerning couples' demographic background and female partners' lifestyle factors and menstrual situation were collected through face-to-face interviews. Body weights and heights were measured for couples, while some medical examinations were made only for female partners, including resting blood pressure, vaginal secretions examination, hemoglobin, serologic hepatitis B virus (HBV) markers and thyroid-stimulating hormone (TSH) detection.

Trained local health professionals used a questionnaire-based survey to complete a standardized family health file for each participating couple and provided medical examinations and preconceptional counselling services. The province of the inspection agency was also recorded. Couples' date of birth and marriage duration, female partners' demographic characteristics (ethnic background, educational

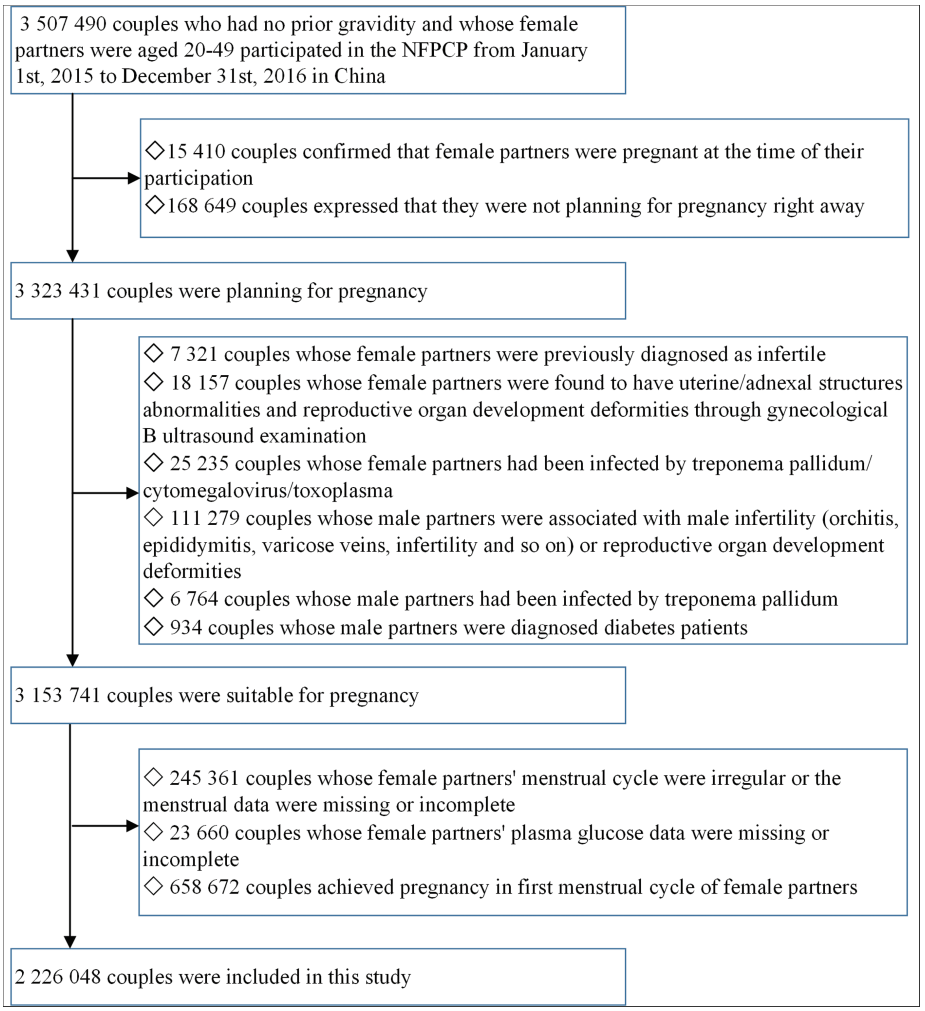

Figure 1 Flowchart for the study population.

level, occupation and household registration), self-reported lifestyle information (alcohol intake and tobacco exposure) and menstrual information (e.g. average menstrual cycle length in the last 6 months, whether menstruation cycle was regular) were collected through face-to-face interviews. Couples' body weights (nearest 0.1 kg) and heights (nearest 0.1 cm) were measured with standardized techniques and protocols after removal of coats, shoes and accessories (He *et al.*, 2016). Experienced physicians conducted blood pressure measurements from the female partner's right arm using an automatic sphygmomanometer after at least 10 min of rest. The results of the female partner's vaginal secretions examination were obtained by vaginal swabs smear microscopy. The female partner's hemoglobin, serologic HBV markers and TSH were tested through blood samples collected after at least 8 h of fasting. The samples were stored at 4°C and analysed within 24 h. Gynecological B ultrasound examination was used to determine the presence of a gestational sac or reproductive organ development deformities by professional doctors at baseline.

Activities at all study sites were implemented with standard operating procedures to ensure reliability of measurements on physical and clinical examinations. The National Center of Clinical Laboratories for Quality Inspection and Detection was responsible for the laboratory external quality assessment biannually and quality control. All data were transferred into the NFPCP medical service information system for storage. The system was developed by the National Research Institute for Family Planning and built with automatic logic checks and instrumental interfaces to avoid human errors.

In this study, a menstrual cycle was defined as the interval between the onset of bleeding in one cycle, accompanied by at least 2 days of bleeding with increased intensity, and the onset of the next similar bleeding episode (Eisenberg *et al.*, 2016). A regular menstrual cycle was defined as a cycle with an intermenstrual interval of 21–35 days, and the variation of cycle length from one period to another was ≤7 days (Doi *et al.*, 2005). Otherwise, it was considered as an irregular menstrual cycle. The age of both female and male partners were measured as continuous variables and further categorized as discrete variables (<24, 25–29, 30–34 and ≥35 years old). Provinces where the inspection agencies were located were grouped into eastern, central and western regions. The 'eastern' region included the provinces of Beijing, Tianjin, Hebei, Liaoning, Shanghai, Jiangsu, Zhejiang, Fujian,

Shandong, Guangdong, Hainan; the 'central' region included the provinces Shanxi, Jilin, Heilongjiang, Anhui, Jiangxi, Henan, Hubei, Hunan; and the 'western' region included the provinces Inner Mongolia, Sichuan, Chongqing, Guangxi, Guizhou, Yunnan, Tibet, Shaanxi, Gansu, Qinghai, Ningxia, Xinjiang (China MoHo, 2013). Marriage duration was defined as the interval years between marriage year and the physical-examination year. Self-reported alcohol intake was defined on two levels: never drinking (No) and any other frequency of drinking (Yes), regardless of whether it was beer, wine or liquor. Active smoking was defined as having at least one cigarette per day, and passive smoking was defined as exposure to environmental tobacco smoke almost every day (in the workplace, home or elsewhere) (Wang *et al.*, 2018b). Given that tobacco particles attach to the smoker's clothing and skin surfaces, persist for a long time and are likely released back into the air, male partners who smoke either indoors or outdoors may carry these tobacco particles and put female partners at risk for tobacco exposure (Jacob *et al.*, 2017). Therefore, we defined female partner's tobacco exposure on two levels: female partner was neither an active/passive smoker and her male partner was not a smoker (No) and otherwise was considered as tobacco exposure (Yes). BMI was calculated using weight and height based on the following formula: BMI = weight/height^2 (kg/m^2). BMI was used to categorize both female partners and male partners into four groups: underweight (<18.5 kg/m^2), normal weight (18.5–23.9 kg/m^2), overweight (24.0–27.9 kg/m^2) and obesity (≥28.0 kg/m^2) (Mi *et al.*, 2015). According to the criteria on the seventh report of Joint National Committee (Chobanian *et al.*, 2003), we defined hypertension as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg. In this study, we considered that female partners had genital tract infection if infected by at least one of the following pathogens: *Gardnerella vaginallis*, candida, trichomonad, *Neisseria gonorrhoeae* or *Chlamydia trachomatis* or had HBV infection if her hepatitis B surface antigen was positive. We categorized serum TSH levels into decreased (<0.44 μmol/L), normal (0.44–3.45 μmol/L) and elevated (>3.45 μmol/L) groups. All of these classifications were determined according to the laboratory guidelines and specifications of the NFPCP and were considered as clinically important in China.

The variables used in multivariable models included demographic characteristics, lifestyle information and clinical examinations. Model A adjusted for some basic demographic characteristics of female partners, including age (continuous), ethnic background (Han/other), educational level (high school or below/bachelor degree or above), occupation (famer/worker/civil servant/other), household registration (rural/urban) and region (eastern/central/western). Model B was based on model A and additionally adjusted for some behavioural habits and health-related indicators of female partners including alcohol intake (yes/no), tobacco exposure (yes/no), BMI (underweight/normal/overweight/obesity), blood pressure (hypertension or no), genital tract infection (yes/no), HBV infection (yes/no), hemoglobin level (<115 g/L/≥115 g/L/) and TSH level (decreased/normal/elevated). Model C was based on model B and additionally adjusted for some covariates including marriage duration (<1 year/1–3 years/>3 years) and male partner's age (continuous) and BMI (underweight/normal/overweight/obesity).

Female partners' FPG levels were also measured by glucose oxidase method at baseline. Based on the World Health Organization guideline (Alberti and Zimmet, 1998), couples were further classified into three groups by female partners' FPG levels: diabetes (FPG ≥ 7.0 mmol/L), IFG (6.1 mmol/L ≤ FPG <7.0 mmol/L) and normal FPG groups (FPG < 6.1 mmol/L). Elevated FPG was defined as FPG ≥ 6.1 mmol/L (thus, including both IFG and diabetes).

Thereafter, health professionals kept in touch with these couples through telephone interviews every 3 months. Pregnancy was assessed by the female partner's self-reported pregnancy outcome that was confirmed by a professional hospital's gynecologic ultrasound. Female partners were urged to recall and report their last menstrual period, whether pregnant or not. All couples were followed up while attempting to become pregnant, until they reported pregnancy or up to 1 year. Data are obtained from the NFPCP whose authors may be contacted by genetic88@sina.com or genetic88@126.com.

TTP in cycles is defined and calculated by the following formula: TTP = [(date of the last menstrual period—date of baseline questionnaire completion)/average menstrual cycle length] + 1. TTP was rounded to the nearest whole number. Thus, TTP was considered censored if the female partner was lost to follow-up or if she was not pregnant after 12 menstrual cycles or at the end of year 2017.

Statistical analysis

Mean (SD) and counts (percentages) were used to describe the baseline characteristics of couples, and one-way ANOVA test and chi-square test were used to examine the group differences of each variable. The cumulative pregnancy rates in each menstrual cycle within each group were estimated by Kaplan–Meier method and shown in the Kaplan–Meier plot.

The Cox models for discrete survival time were used to estimate the fecundability odds ratios (FORs) and their corresponding 95% CIs associated with specific pre-pregnancy maternal FPG levels. FORs estimate the odds of becoming pregnant in the current cycle for a female partner with or without IFG/diabetes, conditional on not being pregnant in the previous cycle. FORs of <1 indicate a reduction in fecundability or a longer TTP, while FORs of >1 indicate a shorter TTP. Models were first run to estimate the crude FORs, then three multivariable models were fit to adjust for potential risk factors of fecundability. Model A was adjusted for some basic demographic characteristics of female partners, model B was additionally adjusted for some behavioural habits and health-related indicators of female partners and model C was further adjusted for some male partners' covariates and couple's marriage duration. Subgroup analyses were also conducted by dividing couples into different subgroups based on the potential risk factors from model C.

Furthermore, the dose–response relationship between pre-pregnancy maternal FPG levels and fecundability were explored by the cubic splines method. Couples were divided into 10 groups based on female partners' FPG levels, so that each group covered a range of 0.5 mmol/L. Model C was used to estimate the adjusted FORs and 95% CIs, with the marginal group (FPG > 8.4 mmol/L) as the reference group.

All analyses were performed using SAS software (SAS version 9.3; SAS Institute, Inc., Cary, NC, USA). Two-sided *P*-values <0.05 were deemed to be statistically significant.

Table 1 Baseline characteristics of study population by classifications of pre-pregnancy maternal fasting plasma glucose levels.

Variables	Diabetes (*n* = 26 071)	IFG (*n* = 65 489)	Normal (*n* = 2 134 488)	Missing
Female partners				
Age, y (mean ± SD)	26.4 ± 4.2	25.9 ± 3.8	25.6 ± 3.5	0
20–24	8777 (33.7)	24 024 (36.7)	847 057 (39.7)	
25–29	12 865 (49.4)	33 014 (50.4)	1067 723 (50.0)	
30–34	3095 (11.9)	6207 (9.5)	170 769 (8.0)	
≥35	1334 (5.1)	2244 (3.4)	48 939 (2.3)	
Ethnic Background				0
Han	22 958 (88.1)	58 088 (88.7)	1926 624 (90.3)	
Others	3113 (11.9)	7401 (11.3)	207 864 (9.7)	
Educational level				91 297
High school or below	18 164 (73.4)	44 086 (70.5)	1450 588 (70.9)	
Bachelor degree or above	6597 (26.6)	18 443 (29.5)	596 873 (29.2)	
Occupation				101 304
Farmer	15 498 (63.1)	37 894 (61.2)	1326 875 (65.1)	
Worker	2618 (10.7)	6550 (10.6)	169 260 (8.3)	
Civil servant	2894 (11.8)	7945 (12.8)	262 199 (12.9)	
Others	3540 (14.4)	9508 (15.4)	279 963 (13.7)	
Household registration				155
Rural	23 122 (88.7)	57 731 (88.2)	1865 571 (87.4)	
Urban	2949 (11.3)	7755 (11.8)	268 765 (12.6)	
Region				0
Eastern	8430 (32.3)	20 220 (30.9)	573 442 (26.9)	
Central	10 310 (39.6)	27 776 (42.4)	956 550 (44.8)	
Western	7331 (28.1)	17 493 (26.7)	604 496 (28.3)	
Alcohol intake	732 (2.8)	2016 (3.1)	65 536 (3.1)	10 486
Tobacco exposure	7390 (28.5)	16 689 (28.7)	567 926 (26.7)	3914
BMI, kg/m^2 (mean ± SD)	21.9 ± 4.6	21.4 ± 4.1	21.0 ± 4.5	11 418
Underweight (<18.5)	3825 (14.8)	9994 (15.4)	349 702 (16.5)	
Normal (18.5–)	16 247 (63.0)	44 096 (68.0)	1535 749 (72.3)	
Overweight (24.0–)	3757 (14.6)	8024 (12.4)	193 949 (9.1)	
Obesity (≥28.0)	1956 (7.6)	2738 (4.2)	44 590 (2.1)	
Hypertension	812 (3.1)	1365 (2.1)	25 937 (1.2)	11 117
Genital tract infection	602 (2.5)	1526 (2.5)	47 220 (2.3)	93 754
HBV infection	1850 (7.1)	4027 (6.2)	102 469 (4.8)	1380
Low hemoglobin (<115 g/L)	2771 (10.7)	6893 (10.6)	203 202 (9.6)	8034
TSH level, μmol/L				22 887
Decreased (<0.44)	1543 (6.00)	3207 (5.0)	68 476 (3.2)	
Normal (0.44-)	21 867 (84.9)	55 305 (85.3)	1841 899 (87.2)	
Elevated (>3.45)	2336 (9.1)	6291 (9.7)	202 237 (9.6)	
Couples				
Marriage duration, y				251 722
<1	17 592 (76.9)	44 031 (76.5)	1321 139 (69.8)	
1–3	3914 (17.1)	10 506 (18.3)	472 181 (24.9)	
>3	1382 (6.0)	3040 (5.3)	100 541 (5.3)	

Continued

Table I *Continued*

Variables	Diabetes (*n* = 26 071)	IFG (*n* = 65 489)	Normal (*n* = 2 134 488)	Missing
Male partners				
Age, y (mean ± SD)	28.3 ± 4.7	27.7 ± 4.2	27.2 ± 3.9	0
20–24	4501 (17.3)	12 649 (19.3)	493 063 (23.1)	
25–29	13 840 (53.1)	37 056 (56.6)	1213 098 (56.8)	
30–34	5249 (20.1)	11 396 (17.4)	324 613 (15.2)	
≥35–	2481 (9.5)	4386 (6.7)	103 714 (4.9)	
BMI, kg/m^2, (mean ± SD)	23.0 ± 3.6	22.9 ± 3.6	23.0 ± 3.5	8862
Underweight (<18.5)	1275 (4.9)	3326 (5.1)	95 626 (4.5)	
Normal (18.5–)	16 453 (63.7)	41 543 (63.9)	1377 245 (64.8)	
Overweight (24.0–)	6318 (24.4)	15 923 (24.5)	524 915 (24.7)	
Obesity (≥28.0)	1801 (7.0)	4182 (6.4)	128 579 (6.1)	

Abbreviations: N, number; IFG, impaired fasting glucose; HBV, hepatitis B virus; TSH, thyroid stimulating hormone. Note: Comparisons among three groups were performed by either ANOVA or chi-square test. All *P*-values were less than 0.001 except for female partners' alcohol intake and male partners' BMI (continuous). Data are *N* (%) unless stated otherwise.

Results

By 31 December 2016, 2 226 048 eligible couples attempting first pregnancy were included in this study (Fig. 1). The average ages of female partners and male partners were 25.6 (SD = 3.5) and 27.2 (SD = 3.9) years, respectively. The prevalence of IFG and diabetes among female partners were 2.94% and 1.17%, respectively. Baseline characteristics of the study population were presented by classifications of pre-pregnancy maternal FPG levels (Table I). Because of the large population, although most baseline characteristics showed statistically significant differences among the three groups (except for female partners' alcohol intake and male partners' BMI), some of these differences between groups were very small.

Overall, 795 968 female partners (35.76%) became pregnant during the study period, and the median TTP was three menstrual cycles (quartile range: 2–5). Among them, 83.05% were pregnant in the first six menstrual cycles. The estimated overall cumulative pregnancy rate for 12 cycles was 41.97%. The reported pregnancy rates reported were low because 658 762 couples who achieved pregnancy during their first menstrual cycle after entering the study were excluded.

In the elevated FPG group, the estimated cumulative pregnancy rate was 34.39% (35.52% in the IFG group and 31.52% in the diabetes group), significantly lower than that of the normal FPG group (42.29%) (overall survival log-rank test, $P < 0.001$) (Table II, Supplementary Fig. S1).

Comparing to the normal FPG group, the crude FORs were 0.80 (95%CI: 0.79–0.81) and 0.69 (95%CI: 0.67–0.71) for the IFG and diabetes groups, respectively. The fully adjusted model (Model C) revealed that female partners with IFG or diabetes had an 18% or 26% lower risk of pregnancy respectively, as compared to the normal FPG group (Table II).

The results from the subgroup analyses are shown in Supplementary Figure S2. The association between pre-pregnancy maternal glucose levels and couples' fecundability did not appear to be modified by baseline characteristics. The diabetes group generally had lower FORs than the IFG group in most subgroups. It was worth noting that the FORs and BMI of female partners were inversely correlated. Among female partners with higher BMI, the negative effect of elevated FPG (either IFG or diabetes) on TTP was more pronounced than those with lower BMI. As for diabetic female partners, FORs decreased when they had hypertension.

Dose–response analysis based on model C showed a non-linear association between the FPG levels and FORs (Fig. 2). The optimal pre-pregnancy maternal FPG level for the shortest TTP was 3.90–4.89 mmol/L, since a couples' fecundability is likely to decrease outside this optimal FPG range (Supplementary Table SI).

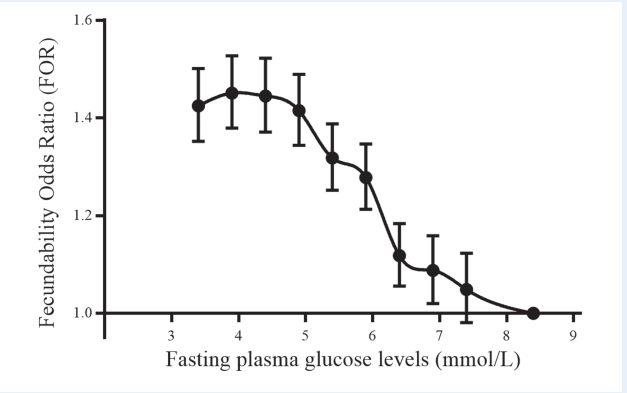

Figure 2 The fitting curve of FORs by different pre-pregnancy maternal FPG levels. The cubic spline was used to fit the curve. The FORs were estimated by discrete-time Cox model adjusting for female partner's age, ethnic background, educational level, occupation, household registration, region, alcohol intake, tobacco exposure, BMI, blood pressure, genital tract infection, HBV infection, hemoglobin level, TSH level, male partner's age and BMI and marriage duration of couples. The error bars represent the 95% CI.

Table II Pre-pregnancy maternal glucose levels were associated with fecundability odds ratios.

Groups	The cumulative pregnancy rate for 12 cycles (%, 95%*CI*)	Crude FOR (95% CI)	Model A FOR (95% CI)	Model B FOR (95% CI)	Model C FOR (95% CI)
Normal	42.29 (42.22–42.37)	Ref	Ref	Ref	Ref
IFG	35.52 (35.11–35.94)	0.80 (0.79–0.81)	0.81 (0.80–0.83)	0.81 (0.80–0.82)	0.82 (0.81–0.83)
Diabetes	31.52 (30.87–32.17)	0.69 (0.67–0.71)	0.72 (0.70–0.74)	0.72 (0.70–0.74)	0.74 (0.72–0.76)

Abbreviations: IFG, impaired fasting glucose; FOR, fecundability odds ratio. Note: Model A was adjusted for female partner's age, ethnic background, educational level, occupation, household registration and region. Model B was additionally adjusted for female partner's alcohol intake, tobacco exposure, BMI, blood pressure, genital tract infection, HBV infection, hemoglobin level and TSH level based on model A. Model C was additionally adjusted for marriage duration, male partner's age and BMI based on model B.

Discussion

In this large cohort of 2 226 048 couples in China, 1.17% female partners were diabetic and 2.94% were IFG. These prevalences were much lower than those reported in other studies (Xu *et al.*, 2013), presumably reflecting the fact that couples in our study were relatively younger and would pay more attention to preconception health while attempting first pregnancy. Elevated pre-pregnancy maternal glucose levels were associated with the couple's lower fecundability and lead to prolonged TTP. Specifically, the FORs were decreased by 26% and 18% in the diabetes and IFG groups, respectively, compared to the normal FPG group. To our knowledge, this is the first large-scale population-based prospective study on the fecundability of pre-pregnancy female partners with diabetes or IFG in China.

The association between female diabetes and fecundability has been studied with mixed findings. A study (Whitworth *et al.*, 2011) based on the Norwegian Mother and Child Cohort including 58 004 women showed that the diabetes would significantly reduce the fecundability. However, only 221 women with type I diabetes and 88 women with type II diabetes were included in this study, and the prevalence of the diabetes (0.53%) was much lower than in our study. Eisenberg *et al.* (2016) used the data from the Longitudinal Investigation of Fertility and the Environment and found that male partners with diabetes could prolong couple's TTP, but the impact of female partners with diabetes on the TTP was not statistically significant. The main limitation of this study was the small sample size, with only 501 couples and 6 diabetic females included in the analysis. Moreover, all of these studies focused on females with diabetes; therefore, the association between females with pre-diabetes or IFG and couple's TTP was not fully elucidated. In the present study, we were specifically interested in the association between fertility and female partners with IFG. This was due to the fact that IFG appears earlier than diabetes, allowing interventions through healthy diet and regular exercise as early as possible to improve both maternal and infant health.

The findings from these population-based studies have aroused interest in studying the underlying mechanisms linking diabetes and infecundity. Ou *et al.* (2012) used mouse models and found that maternal insulin resistance causes oxidative stress and mitochondrial dysfunction in oocytes and impairs the oocyte size and maturation. In addition, the hypothalamic–pituitary–ovarian axis is the main regulation mechanism of women's menstrual cycle and may be affected by the glucose levels (Livshits and Seidman, 2009). An insulin disorder might also account for polycystic ovarian syndrome (PCOS) (Gandhi *et al.*, 2017) and some menstrual problems relating to fecundability. A recent meta-analysis (Kakoly *et al.*, 2018) indicated that PCOS is associated with impaired glucose tolerance and type II diabetes mellitus. Meanwhile, PCOS is an identified risk factor for female infertility, indicating a causal relationship among diabetes, PCOS and infertility. Although we excluded female partners who might have PCOS (through ultrasonography) when they participated in the NFPCP, as well as those female partners with irregular menstruation, the underlying pathological and physiological changes are not easily observed. These dynamic changes might still influence the interpretation of fecundability. Diabetes is also reported to be related to dyspareunia (such as lower sexual desire and more pain during sex) (Afshari *et al.*, 2017), which might potentially decrease the frequency of sexual intercourse, thus lead to lower fecundability.

Our study had multiple strengths, including the large population-based sampling framework and use of standardized data collection methods and strict laboratory quality control to ensure the reliability of the data. In addition, as a prospective study, all eligible couples attempting first pregnancy were included, so response and recalling biases were minimal. Meanwhile, the medical intervention bias was also considered to be low, as the fertility of these couples was not affected by previous pregnancies (Joffe *et al.*, 2005). Finally, we included only couples who were planning for pregnancy and excluded those couples who became pregnant during the first menstrual cycle, thus minimizing the planning bias in this study (Joffe *et al.*, 2005).

Nevertheless, our study had unavoidable limitations. First, there was potential bias in the TTP calculation. We were lacking available data regarding the time couples had spent in attempting pregnancy prior to study enrollment, which would underestimate the TTP. In contrast, if some couples had certain uncontrolled or untreated medical conditions or emergencies, they might temporarily stop attempting pregnancy without informing us during telephone interviews, which would overestimate the TTP. Second, the pregnancy rate of our cohort was relatively low; thus our results might not generalize to other reproductive populations. Possible explanations regarding the low pregnancy rate, apart from the exclusion of couples who became pregnant during the first menstrual cycle, were the inability to obtain timely information and possible bias in reporting pregnant outcome (some couples who had a miscarriage in follow-up intervals were reluctant to report this situation) (Boland *et al.*, 2006). Furthermore, we only defined clinical pregnancy based on the female partner's self-reported ultrasound

evaluation and did not include biochemical pregnancy (Kolte *et al.*, 2015) as part of the criterion for pregnancy. Third, we only used a single FPG test at baseline to define diabetes or IFG, and we were unable to obtain the subsequent diagnostic data (such as oral glucose tolerance and glycosylated hemoglobin test) throughout the follow-up period, which might create classification bias. Fourth, although we had strict exclusion criteria and adjusted as many covariates as possible, we did not collect all relevant data associated with the couples' fertility, such as male partners' FPG, semen quality and frequency of intercourse. Fifth, because we categorized some covariate variables in the model fit, they were sacrificed to potentially lose information and eventually might lead to implausible regression interpretations (Altman and Royston, 2006, Royston *et al.*, 2006). Finally, the findings should be cautiously extrapolated to a general population because our study was limited to couples at younger ages who were trying to conceive for the first time.

In summary, elevated pre-pregnancy maternal glucose levels were associated with prolonged TTP among couples with no prior gravidity in China. These findings highlighted the great public health significance in promoting early evaluation and preventive treatment for IFG or diabetic women by pre-pregnancy examination to improve population fecundability.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

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Authors' roles

Supervision of the study and financial support: X.M. and B.W.; data analysis and results interpretation: J.Z., X.H., Q.D., K.H., X.Z. and Y.L.; literature retrieval and manuscript drafting: J.Z. and X.H.; project execution and data collection: Q.W., H.S., Z.X., Y.Z. (Yiping Zhang) and D.Y.; data management: H.Z.; methodological guidance: J.W.; manuscript revision: J.Z., X.H., J.W., D.Q., X.Y. and Y.Z. (Yue Zhang).

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Conflict of interest

None declared.

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