Title: The impact of maternal pre-pregnancy impaired fasting glucose on preterm birth and large for gestational age: a large population-based cohort study

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Condensation: Maternal pre-pregnancy impaired fasting glucose increases the risk of preterm birth and larger for gestational age

Short title: Impact of pre-pregnancy impaired fasting glucose on preterm birth and large for gestational age

AJOG at a Glance

A. Little is known about the impact of maternal pre-pregnancy impaired fasting glucose (IFG) on preterm birth (PTB) and large for gestational age (LGA).
B. In this large cohort study, we found that compared with women with normoglycaemia, women with pre-pregnancy IFG had 7.0%, 10.0% and 17.0% higher risk of PTB, LGA and severe LGA, these associations were similar in subgroups of women with various baseline characteristics. Fasting glucose below the WHO cut-point for IFG also increased the risk of LGA and severe LGA.
C. Our data, for the first time, indicated that maternal pre-pregnancy IFG increases the risk of PTB, LGA and severe LGA. WHO cut-point of IFG is too restrictive and lesser levels of fasting glucose also increase the risk of LGA and severe LGA.

ABSTRACT

Background The impact of maternal pre-pregnancy impaired fasting glucose on preterm birth and large for gestational age has been poorly understood.

Objectives We aimed to estimate the impact of pre-pregnancy impaired fasting glucose defined by the WHO cut-point on the risk of preterm birth and large for gestational age, and to investigate whether the WHO cut-point of impaired fasting glucose was appropriate for identifying women at the risk of preterm birth and large for gestational age among the Chinese population.

Study Design This was a retrospective cohort study of women from the National Free Preconception Health Examination Project with singleton birth from 121 counties/districts in 21 cities of Guangdong Province, China, from 1st January 2013 to 31st December 2017. Women were included if pre-pregnancy fasting glucose was less than 7.0mmol/L. The primary outcomes were preterm birth (gestational age <37 weeks), early preterm birth (gestational age <34 weeks), large for gestational age (birth weight by gestational age >90th percentile based on the international standards in the INTERGROWTH-21st) and severe large for gestational age (birth weight by gestational age >97th percentile). We calculated the adjusted risk ratio for impaired fasting glucose, and a 1 standard deviation increase in fasting glucose.

Results We included 640469 women. Of these, 31006 (4.84%) met the WHO cut-point for impaired fasting glucose, 32640 (5.10%) had preterm birth and 7201 (1.12%) had early preterm birth, 45532 (7.11%) had large for gestational age birth and 16231 (2.53%) had severe large for gestational age birth. Compared with women with normoglycaemia, women with pre-pregnancy impaired fasting glucose had a 7.0% higher risk of preterm birth (adjusted risk ratio 1.07, 95%CI 1.02-1.12), 10.0% higher risk of large for gestational age

(1.10, 1.06-1.14) and 17.0% higher risk of severe large for gestational age (1.17, 1.10-1.26). No significant association of pre-pregnancy impaired fasting glucose with early preterm birth was found. The association of pre-pregnancy impaired fasting glucose with preterm birth and large for gestational age were similar in subgroups of women with various baseline characteristics. Adjusted risk ratio for preterm birth per standard deviation fasting glucose (0.7mmol/L) was 0.99 (95% CI 0.98-1.00), for early preterm birth 0.99 (0.97-1.02), for large for gestational age 1.04 (1.03-1.05) and for severe large for gestational age 1.03 (1.01-1.04).

Conclusions Our data suggest that maternal pre-pregnancy impaired fasting glucose increases the risk of preterm birth, large for gestational age and severe large for gestational age. Data also suggest that the WHO cut-point of impaired fasting glucose is too restrictive and lesser levels of fasting glucose also increase the risk of large gestational age and severe for severe gestational age in the Chinese population. Further investigation is warranted to determine whether and how counselling and interventions for women with pre-pregnancy impaired fasting glucose could reduce the risk of preterm birth and large for gestational age.

Keywords Cohort Study; Impaired Fasting Glucose; Large for Gestational Age; Large Scale; Preterm Birth; Pre-pregnancy

Introduction

Preterm birth (PTB) is the leading cause of death for children below 5 years of age globally.[1] The estimated global PTB rate was 10.6%, equal to an estimated 14.84 million live PTBs in 2014.[2] PTB complications are estimated to be responsible for 35% of deaths among neonates annually, and surviving preterm neonates are at higher risk of respiratory and neurodevelopmental complications.[3] Large for gestational age (LGA), found in 9% to 13% of all deliveries, is also associated with multiple risks for both the maternally and the neonates.[4] Short term risks of LGA include a two to three fold increase in intrauterine death rate[5], a higher probability of operative delivery and several neonatal morbidities, such as shoulder dystocia, obstetric brachial plexus injury and birth fractures and increased risk of trauma to the mothers.[6] There are also long-term risks for neonates, such as obesity, metabolic syndrome, and chronic disease in later life.[7,8] Both PTB and LGA are associated with significant costs to health services, and families of PTB and LGA often experience considerable psychological and financial hardship.[1,9,10] These data highlight the critical and urgent need to identify risk factors of PTB and LGA.

The association of diabetic pregnancy with PTB and LGA is well documented.[11-13] However, little is known about the impact of maternal pre-pregnancy impaired fasting glucose (IFG, typically defined as fasting glucose levels that are above normal but below diabetic fasting glucose threshold[14]) on PTB and LGA. From the perspective of health management and disease prevention, to identify the impact of pre-pregnancy IFG on PTB and LGA are of substantial public health importance since it might be relatively easy to implement health interventions, and more helpful to decrease the risk of PTB and LGA for women who had IFG before pregnancy.[15,16]

In this study, we aimed to investigate the impact of pre-pregnancy IFG on PTB and LGA within a large cohort study from Southern China. We also aimed to investigate whether the current cut-point of IFG as recommend by the WHO, which was primarily designed to identify population who are at greater risk for developing micro- and macrovascular complications and diabetes, was appropriate for identifying women at risk of PTB and LGA in China.

Material and Methods

Study participants

This study was embedded within the framework of the National Free Preconception Health Examination Project (NFPHEP), launched by the Chinese National Health and Family Planning Commission and the Ministry of Finance in 2010. The NFPHEP has covered all rural counties/districts in China since 2013. The project aims to reduce adverse pregnancy outcomes through providing free health examination before conception, counselling services for reproductive couples who plan to conceive within the next six months and follow up of pregnancy outcomes in the households registered as agricultural residents and the migrant population who have lived in the local area for more than six months. Project-related design, organization, and implementation have been described previously.[17-19]

We conducted a retrospective cohort study of 728114 women of reproductive age who participated in the NFPHEP from 1st January 2013 to 31st December 2017, who successfully conceived and then had pregnancy outcomes from 121 counties/districts in 21 cities in Guangdong Province, China.

For the purpose of this study and similar to the previous study,[20] we developed the exclusion criteria. Specifically, we excluded women who did not measure fasting serum

glucose (FSG) before pregnancy; women with chronic disease (including anaemia, hypertension, heart disease, hepatitis B, epilepsy, thyroid disease, chronic nephritis, cancer and diabetes); women with newly diagnosed hypertension (systolic blood pressure (SBP)≧140mmHg or diastolic blood pressure (DBP)≧90mmHg), and newly diagnosed diabetes (FSG≧7.0mmol/L). Women with multiple births or post-term pregnancies (gestation age >42 weeks), and with outcomes of miscarriages, induced abortions, birth defects or stillbirths were also excluded.

The NFPHEP was approved by the Institutional Review Board of the Chinese Association of Maternal and Child Health Studies. Written informed consent was obtained from the participants before recruitment. The present study was executed jointly by the Guangdong Institute of Family Planning Science and Technology and Guangzhou Medical University, in which the review boards determined that this study was exempt for ethical approval owing to the use of de-identified data.

Procedures

Baseline

The program was based on the primary health and family planning network. All the reproductive couples who had planned to conceive and were willing to participate in NFPHEP were recruited. Baseline information of participated couples was collected by trained local community staff with a structured questionnaire. The questionnaire included demographic characteristics (age, educational level, occupation, ethnicity, migration and address of residence), history of chronic disease (hypertension, diabetes, heart disease, chronic nephritis, anaemia, cancer and psychiatric diseases), history of pregnancy (gravidity and parity) and history of adverse pregnancy outcomes (preterm birth, miscarriage, induced abortion, birth defect and stillbirth), lifestyle (maternal active smoking, passive smoking,

alcohol consumption and husband smoking). Completeness of the questionnaire was reviewed, and data were then entered into the web-based data collection system, which was then gathered into the Guangdong Institute of Family Planning Science and Technology. Clinical professionals from the local authorized medical institutions then did physical examinations and collected blood samples. Body weight, height and blood pressure were measured by calibrated instruments and standard specifications. Fasting peripheral venous blood samples (not eating anything for at least 8 hours) were collected with the tube containing a rapidly effective glycolysis inhibitor, and immediately taken back for measurement in accredited laboratories that are affiliated to local authorized medical institutions.

Serum samples were separated and used for analysing FSG concentration within two hours of arrival at local laboratories. FSG concentrations were analysed by using an automatic biochemistry analyser with the corresponding reagents kits, all of which were certified by the China Food and Drug Administration. The Centre of Clinical Laboratories for Quality Inspection and Detection of Guangdong Institute of Family Planning Science and Technology was responsible for external quality assessment semi-annually and for quality control.[21] Interclass correlation coefficients expressing between-person variance as a percentage of the total variance, obtained by analysis of replicate pairs of samples drawn at baseline from all the counties involved were all higher than 0.98 for FSG concentration.

Follow up

After the pre-pregnancy physical examination, all the participated women were followed up by trained local community staff by telephone every two months to determine whether they had conceived successfully. Local community staff also interviewed the women face to face or by telephone within three months after conception, recording their last menstrual

period, active smoking, alcohol consumption, and husband smoking during the early stage of the pregnancy. Mothers were also interviewed face to face or by telephone within six weeks of delivery to collect information on the hospital where they gave birth. Local community staff then collected data from the medical records at the reference hospital regarding pregnancy outcomes, including current pregnancy outcomes (normal birth, preterm birth, miscarriage, induced abortion, stillbirth or birth defects), gestational age (weeks), birth weight (grams) and neonatal information (singleton or multiple births). The endpoint of this study was to observe the pregnancy outcomes of the participated mothers and the study was terminated on 31st December 2017.

Definition and ascertainment of IFG

Previous study has suggested that FSG concentration is equal to fasting plasma glucose (FPG) concentration,[22] both of which could be used to screen and diagnose intermediate hyperglycaemia or diabetes.[23] Based on WHO guidelines, [24] IFG was defined as FSG concentration of 6.1 mmol/L or greater and lower than 7.0 mmol/L, except for those who either reported previously diagnosed diabetes or used blood glucose-lowering drugs. Information about previously diagnosed diabetes and the use of blood glucose-lowering drugs was obtained from the structured questionnaire. After excluding previously diagnosed and newly diagnosed diabetes, we then divided the participants into two groups according to their pre-pregnancy FSG concentration: women with IFG and women with normoglycemia (FSG<6.1mmol/L).

Outcomes

The primary outcomes were PTB, early PTB, LGA, and severe LGA. PTB was defined as births delivered at gestational age less than 37 weeks and early PTB as births delivered at

gestational age less than 34 weeks. Gestational age was calculated from the first day of the last menstrual period, which was measured by ultrasound at the first trimester of pregnancy. Based on the international standards in the INTERGROWTH-21st Project, LGA was defined as birth weight by gestational age and gender beyond the 90th percentile, and severe LGA as birth weight by gestational age and gender beyond the 97th percentile.[25]

Statistical analysis

Medians and interquartile range (IRQ) were calculated for age. Frequencies and proportions were used to describe the baseline characteristics of the participants and the four outcomes among the participants by different baseline characteristics or different categories of fasting glucose levels. Chi-square tests were employed to compare the distribution of pre-pregnancy status of IFG according to different baseline characteristics.

Log-binomial models based on Generalized Estimating Equations (GEE) were employed to estimate the adjusted risk ratios (aRRs) and 95% CIs of PTB and LGA for women with pre-pregnancy IFG, and different covariates were adjusted in three models to examine the robustness of our findings. We adjusted for sociodemographic characteristics of participants in model 1, including age at baseline (19-24 years, 25-29 years, 30-34 years, 35-39 years, or 40-50 years), ethnicity (Han or others), educational level (primary school or below, junior high school, senior high school or college or above), occupation (farmer, worker, servicer or others), region (pearl river delta, non-pearl river delta), and migrant population (yes or no). In model 2, we additionally adjusted for covariates of history of pregnancy and adverse pregnancy outcomes, including first pregnancy (yes or no), primipara (yes or no); history of PTB (yes or no), miscarriage (yes or no), induced abortion (yes or no), birth defects (yes or no), or stillbirths (yes or no). In model 3, we additionally adjusted for body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters) categories of

women before pregnancy (underweight: <18.5kg/m^2, normal weight: 18.5-24kg/m^2, overweight: 24-28kg/m^2, or obesity: ≥28kg/m^2),[26] smoking status of husband before pregnancy and during the early stage of pregnancy (yes or no), smoking and alcohol consumption of women before pregnancy and during the early stage of pregnancy (yes or no), and passive smoking of women before pregnancy (yes or no).

We conducted sensitivity analysis with additional adjustment for the length of time from pre-pregnancy examination to the last menstrual period (continuous data) or inclusion of women with self-reported perceived economic pressure (yes or no). We further used subgroup analysis to examine the aRRs and 95% CIs of PTB and LGA for women with the pre-pregnancy IFG among different subgroups on the basis of baseline characteristics. Among all the subgroup analysis, we adjusted for the most covariates.

We examined the impact of fasting glucose levels on PTB and LGA by categories, and with fasting glucose as a continuous variable (per SD) to determine whether the WHO cut-point of IFG was appropriate for identifying women at risk of PTB and LGA. We followed the analytical protocol used in the Hyperglycaemia and Adverse Pregnancy Outcomes (HAPO) study,[27] fasting glucose was divided in to seven categories with ~50% of all values in the two lowest categories and 3% and 1% in the two highest categories, respectively (see Table 3 and Figure C.1 footnotes for definition of categories).

Data were missing in first pregnancy (2729, 0.4%), primipara (2729, 0.4%), body mass index (6439, 1.0%), active smoke before pregnancy (4452, 0.7%), passive smoke (4419, 0.7%), husband smoke before pregnancy (22312, 3.5%), alcohol before pregnancy (6084, 0.9%), active smoke during early-stage pregnancy (21140, 3.3%), husband smoke during early-stage pregnancy (21618, 3.4%), alcohol during early-stage pregnancy (21664, 3.4%). We imputed these missing covariates by using the multiple imputation methodology based on

other socio-demographic covariates. The significance level was set at 0.05 and all tests were two-sided. Statistical analyses were conducted by using Stata (Version 14.0) and Statistic software R (version 3.5.2).

Results

Participant characteristics

We excluded 7996 women who did not measure fasting serum glucose (FSG) before pregnancy; 31502 women with chronic disease; 7987 women with newly diagnosed hypertension; and 2995 women with newly diagnosed diabetes. We also excluded 24073 women who had miscarriages, induced abortions, birth defects or stillbirths and 13092 women with multiple births or post-term pregnancies (gestation age≧42 weeks). The remaining 640469 participants were included in the final analysis. Figure 1 shows the selection of participants for the present study. 44.5% of the women included were from nine cities in the Pearl River Delta and 10.2% were migrant populations. The sample size and the proportion of the migrant population in each city are shown in Table A.1. The age of the participants included in the study ranged from 19 to 50 years, the median age was 26 years (IQR 24-29), and 6.2% of the women were older than 35 years. 44.0% of the participants had an educational level of junior high school or below, 34.1% and 30.0% had an occupation of farmer or worker, 99.3% was Han nationality, and 65.3% were in their first pregnancy.

Overall, 31006 (4.84%, 95%CI 4.79%-4.89%) women met the criteria of IFG recommend by the WHO. Compared with those women with normoglycemia, women with IFG were more likely to be living in the non-Pearl River Delta, migrant population, first pregnancy, and primipara, overweight and obesity, and had active or passive smoke exposure before pregnancy (Table 1).

Impact of pre-pregnancy IFG on PTB, early PTB, LGA, and severe LGA

The median length of time from pre-pregnancy examination to the last menstrual period was 3.1 months (IQR 1.7-5.2). 32640 of 640469 participants had PTB; the PTB rate was 5.10% (95%CI 5.04%-5.15%) among all the singleton birth. The PTB rate was 5.08% (5.02%-5.13%) among women with normoglycemia and 5.45% (5.20%-5.70%) among women with pre-pregnancy IFG. 7201 participants had early PTB (1.12%, 1.10%-1.15%), which occurred in 6877 (1.13%, 1.10%-1.15%) women with normoglycemia and 324 (1.04%, 0.93%-1.16%) in women with pre-pregnancy IFG.

Among 640469 included singleton births, 45532 births were LGA, and the LGA rate was 7.11% (7.05%-7.17%). 43074 (7.07%, 7.00%-7.13%) LGA births occurred in women with normoglycemia, 2458 (7.92%, 7.62%-8.22%) LGA births occurred in women with pre-pregnancy IFG. 16231 (2.53%, 2.50%-2.57%) births were severe LGA, which occurred in 15294 (2.51%, 2.47%-2.55%) women with normoglycemia and 937 (3.02%, 2.83%-3.21%) women with pre-pregnancy IFG.

The unadjusted and adjusted RRs are shown in Figure A.1. In the fully adjusted model (model 3), compared with women with normoglycemia, women with pre-pregnancy IFG had a 7.0% higher risk of PTB, 10.0% higher risk of LGA births and 17.0% higher risk of severe LGA births (Table 2). However, no significant association of IFG with early PTB was found. In all the three models of PTB, early PTB, LGA, and severe LGA, the aRRs did not substantially change.

Sensitivity and subgroup analyses

In the sensitivity analyses, the impact of pre-pregnancy IFG on PTB and LGA did not substantially change with additional adjustment for the length of time from pre-pregnancy

examination to last menstrual period (Table B.1) or inclusion of women self-reported with perceived economic pressure (Table B.2).

In the subgroup analyses, the impact of pre-pregnancy IFG on the risk of PTB did not appear to be modified by the baseline characteristics (Figure B.1), except that the impact was higher among those living in non-Pearl River Delta or residents versus migrants or Han ethnicity. The impact of pre-pregnancy IFG on the risk of LGA neither appeared to be modified by the baseline characteristics (Figure B.2), except that the impact was greater among those living in Pearl River Delta, with multigravida, multipara or with obesity and exposure to passive smoking before pregnancy.

Is WHO cut-point of fasting glucose appropriate for identifying women at risk of PTB and LGA

The unadjusted percentage of women in each group that had each outcome by category of fasting glucose is shown in Figure C.1. Generally, the frequencies of four outcomes show an increasing trend across the seven categories of fasting glucose except for PTB and early PTB. The higher prevalence of LGA and severe LGA is consistent across all fasting glucose categories. From the 4^{th} to 7^{th} category, the risk of LGA and severe LGA showed monotonic associations with fasting glucose, while the lowest frequencies of PTB occurred in fasting categories 2, 3 and 4.

Log-binomial models analysis confirmed monotonic associations of fasting glucose with the risk of LGA and severe LGA (Table 3). The associations of the four outcomes with fasting glucose as a continuous variable suggest stronger associations of fasting glucose levels with LGA and severe LGA than that with PTB and early PTB. WHO cut point of IFG is too restrictive and lesser levels of fasting glucose also associated with an increased risk of LGA and severe LGA.

Comment

This is the first study examined the impact of maternal pre-pregnancy IFG on PTB and LGA in a large-scale cohort study, which also investigated whether the WHO cut-point of IFG is appropriate for identifying women at risk of PTB and LGA. In this study, we found that pre-pregnancy IFG increases the risk of PTB, LGA, and severe LGA by 7.0%, 10.0%, and 17.0%, respectively, and the impact is consistent for the various subgroups of women with various baseline characteristics. We also found that WHO cut-point for IFG is too restrictive and lesser levels of fasting glucose also increase the risk of LGA and severe LGA.

In relation to other study

Although there were inconsistent results in terms of the associations of pregnancy hyperglycaemia/diabetes with some adverse pregnancy outcomes (such as PTB) in previous studies,[28,29] it is now well accepted that reducing blood glucose in pregnancy reduces the adverse pregnancy and postpartum complications. It was unexpected that there were very few studies have investigated the impact of pre-pregnancy hyperglycaemia on adverse pregnancy outcomes. To our knowledge, only two studies among the few studies pertaining to pre-pregnancy IFG and adverse pregnancy outcomes.[30,31] Salman and colleagues analysed singleton pregnancies of 1945 women in Israel, but they only found the association of pre-pregnancy IFG with abnormal glucose challenge test (GCT) and gestational diabetes mellitus (GDM), rather than with increased risk of PTB and LGA.[30] Hu and colleagues conducted a prospective study of 16,890 women in central China to estimate the incidence of PTB and identify maternal risk factors before pregnancy from 2010 to 2013.[31] Although they found that women with pre-pregnancy hyperglycaemia (FBG level >6.1mmol/L) had an increased risk of PTB compared with women with normoglycaemia (3.9mmol/L or greater and

6.1mmol/L or less) after adjustment (6.3% vs. 3.6%, aOR 1.69, 1.09-2.62), the definition of hyperglycaemia in this study was unclear, which reduced the strength of the study.[31]

The discrepancies of the associations of IFG or hyperglycaemia both before and during pregnancy with the risk of PTB and LGA might be related to the measurement of blood glucose and the threshold for hyperglycaemia. Evidence from the recent meta-analyses showed that there was a positive linear association with LGA for all glucose exposures across the distribution of glucose concentrations during pregnancy, and no clear evidence of a threshold. However, fasting glucose concentration was inversely association with PTB (aOR 0.77, 95%CI 0.62-0.96), whereas the association between post-load concentration and PTB was more inconsistent: weakly positive for 50g 1-hour oral glucose challenge test (OGCT) or 75g 2-hour oral glucose tolerance test (OGTT), and inverse with 100g 2-hour OGTT.[13] In our study, we also found linear associations of fasting glucose with LGA and severe LGA but not PTB, suggesting a possible threshold of pre-pregnancy fasting glucose for identifying women who had increased risk of LGA. Of noting, although there was no linear association of fasting glucose with PTB, we found inverse associations in fasting glucose categories 2, 3 and 4, which suggested categories 1, 5, 6, and 7 are associated with an increased risk of PTB if we take categories 2, 3 and 4 as the reference.

Explanations of pre-pregnancy IFG associated with increased risk of PTB and LGA

The causes of PTB and LGA are complex and multifactorial. However, the impact of pre-pregnancy IFG on PTB and LGA could be explained by the following aspects. First, IFG is associated with impaired insulin secretion and impaired suppression of hepatic glucose output, and is associated with progressively greater risk of developing micro- and macrovascular complications and then associated with an increased risk of diabetes, which are the identified risk factors of PTB and LGA.[32] Second, pre-pregnancy IFG or

hyperglycaemia is associated with an increased risk of GDM, which might increase the risk of placental inflammation, a known pathogenesis of LGA and a known contributor to PTB.[33] Other conditions developed from pre-pregnancy IFG or hyperglycemia might also lead to PTB and LGA, such as pre-eclampsia and hypertensive associated conditions (such as intrauterine growth restriction and placental abruption).[34] Additionally, the persistent IFG or hyperglycaemia in the placenta transports to the fetus that stimulates islet β-cell proliferation and leads to further hyperinsulinemia, which is also a known contributor to LGA.[35] Third, previous studies reported that women with IFG or hyperglycemia had higher levels of insulin-like growth factor I (IGF-I), which has the function of promoting placental nutrient transfer to enhance fetal growth.[36] Overall, these possible explanations of pre-pregnancy IFG or hyperglycemia associated with increased risk of PTB and LGA might be similar to that of diabetes and GDM or gestational hyperglycemia, because pre-pregnancy blood glucose level and glucose tolerance are the basis of blood glucose level and glucose tolerance during pregnancy, which usually elevates during the pregnancy. Further studies on the potential mechanisms of IFG or hyperglycemia related to PTB and LGA are therefore needed.

Strengths and weakness of this study

The major strength of this study is the sample size. For this cohort, we recruited 640469 participants and followed up pregnancy outcomes with strict quality controls. The number of IFG or fasting glucose categories and events per baseline variables or each fasting glucose categories were enough that the multivariable regression models were not over-fitted.[20] The large sample size allowed us to verify the robust associations of pre-pregnancy IFG with increased risk of PTB and LGA among different subgroups on the basis of baseline characteristics. Additionally, it is also the first explorative study that investigated whether the

WHO cut-point of IFG is appropriate for identifying women who are at risk of PTB and LGA.

The study has some limitations. First, a 2-hour glucose level was not measured in the NFPHEP project. Women who met the criteria for diabetes might be included and misclassified to the IGF group, which could lead to the overestimation of associations of IFG with PTB and LGA. However, the prevalence of IFG estimated was similar to a previous study among Chinese women of reproductive age.[15] Second, some important information on pregnancy complications and obstetrics were missing too much or not collected in the NFPHEP. For example, data on gestational hypertension and diabetes were missing in 99.1% of participants, and data on gestational weight gain and causes of PTB (spontaneous versus indicated) were not collected, both of which make the interpretation of our results difficult. Thus, further studies are warranted to fully understand the impact of pre-pregnancy IFG on IFG and LGA. Furthermore, we were not able to explore the effects of family income on PTB and LGA as such information also was lacking for the vast majority of women. However, the aRRs did not change substantially after additionally adjusting for economic pressure, which is correlated with family income.[37] Third, we may have underestimated the associations of IFG with LGA because lower prevalence rate of LGA in our study, which may not only due to the use of the INTERGROWTH-21st standards, but also due to some policy interventions implemented in China, such as maternal system health care policy that has covered more than 95% pregnant and monitored several risk factors for adverse outcomes during the pregnancy.[38] Finally, although this is a large scale cohort study, the socio-demographic characteristics, economic, culture, nutritional models and medical service level could not be representative of other countries and regions, suggesting that results from the present study should be verified in different population.

Implications

Our findings have important clinical and public health implications. Both PTB and LGA drive the need for neonatal and obstetric care and are related to neonatal and maternal mortality and morbidity. Whilst there is a health burden, clinicians and health professionals pay less attention to IFG screening and interventions due to lack of conclusive evidence on associations of pre-pregnancy IFG with PTB and LGA. Our findings from 640,469 women confirmed a statistically significant increase in risk estimate by 7.0% of PTB, 10.0% of LGA and 17.0% of severe LGA in those women with pre-pregnancy IFG defined by the WHO cut-point compared with those women with normoglycaemia. This suggested that screening for IFG before pregnancy and taking interventions, such as diet, weight control and physical exercise to control fasting glucose before pregnancy,[15,16] might be necessary for reducing the risk of PTB, LGA, and severe LGA. The finding also suggested that WHO cut-point for IFG is restrictive and lesser levels of pre-pregnancy fasting glucose also increase the risk of LGA and severe LGA. Overall, to prevent the risk of PTB, LGA and severe LGA, clinicians and health providers should carry out continuous management of blood glucose both before and during pregnancy.

Conclusion

In conclusion, for the first time, in this large retrospective cohort study, pre-pregnancy IFG defined by the WHO cut-point increases the risk of PTB, LGA, and severe LGA, and the WHO cut-point for IFG is restrictive and lesser levels of fasting glucose also increase risk of LGA and severe LGA. The NFPHEP potentially offers a unique platform to identify women with pre-pregnancy IFG. However, the WHO cut-point of IFG is not appropriate for identifying women at risk of LGA and PTB, and further investigation is warranted to

determine whether and how counselling and interventions for women with IFG before pregnancy can reduce the risk of PTB and LGA.

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Table 1. Maternal baseline characteristics with respect to pre-pregnancy status of FSG

	Pre-pregnancy status of FSG		Total	PTB	Early PTB	LGA	Severe LGA
	Normoglycemia (n=609463)	IFG (n=31006)	(n=640469)	(n=32640)	(n=7201)	(n=45532)	(n=16231)
Region							
Pearl river delta	272992(44.8%)	11916(38.4%)	284908(44.5%)	14986(45.9%)	3449(47.9%)	21333(46.9%)	7563(46.6%)
Non-Pearl River delta	336471(55.2%)	19090(61.6%)	355561(55.5%)	17654(54.1%)	3752(52.1%)	24199(53.2%)	8668(53.4%)
Migrant population							
Yes	617622(10.1%)	3532(11.4%)	65154(10.2%)	3204(9.8%)	728(10.1%)	5767(12.7%)	2067(12.7%)
No	547841(89.9%)	27474(88.6%)	575315(89.8%)	29436(90.2%)	6473(89.9%)	39765(87.3%)	14164(87.3%)
Age at baseline (years)							
19~24	209143(34.3%)	10055(32.4%)	219198(34.2%)	11125(34.1%)	2504(34.8%)	13613(29.9%)	5006(30.8%)
25~29	273151(44.8%)	13824(44.6%)	286975(44.8%)	13982(42.8%)	3029(42.1%)	19710(43.3%)	7048(43.4%)
30~34	90314(14.8%)	4894(15.8%)	95298(14.9%)	5080(15.6%)	1139(15.8%)	8139(17.9%)	2879(17.7%)
35~39	31776(5.2%)	1863(6.0%)	33639(5.3%)	2063(6.3%)	433(6.0%)	3439(7.6%)	1094(6.7%)
40~50	5079(0.8%)	370(1.2%)	5449(0.9%)	390(1.2%)	96(1.1%)	631(1.4%)	204(1.3%)
Education							
Primary school or below	13558(2.2%)	809(2.6%)	14367(2.2%)	738(2.3%)	161(2.2%)	879(1.9%)	305(2.5%)
Junior high school	254231(41.7%)	13542(43.7%)	267773(41.8%)	14560(44.6%)	3270(45.4%)	18778(41.2%)	7021(43.3%)
Senior high school	161776(26.5%)	7815(25.2%)	169591(26.5%)	8234(25.2%)	1773(24.6%)	11584(25.4%)	4071(25.1%)
College or above	179898(29.5%)	8840(28.5%)	18738(29.5%)	9108(27.9%)	1997(27.7%)	14291(31.4%)	4834(29.8%)
Occupation							
Farmer	207175(34.0%)	11054(35.6%)	218229(34.1%)	11791(36.1%)	2586(35.9%)	15194(33.4%)	5592(34.5%)

Worker	182967(30.0%)	9243(29.8%)	192210(30.0%)	9989(30.6%)	2263(31.4%)	13153(28.9%)	4647(28.6%)
Servicer	83207(13.7%)	4049(13.1%)	87256(13.6%)	3857(11.8%)	824(11.4%)	5856(12.9%)	2064(12.7%)
Others	136114(22.3%)	6660(21.5%)	142774(22.3%)	7003(21.5%)	1528(21.2%)	11329(24.9%)	3928(24.2%)
Ethnicity							
Han	605440(99.3%)	30776(99.3%)	636216(99.3%)	32408(99.3%)	7139(99.1%)	45159(99.2%)	16105(99.2%)
Other	4023(0.7%)	230(0.7%)	4253(0.7%)	232(0.7%)	62(0.9%)	373(0.8%)	126(0.8%)
History of pregnancy and adverse pregnancy outcomes							
History of preterm	1818(0.3%)	66(0.2%)	1884(0.3%)	241(0.7%)	67(0.9%)	178(0.4%)	53(0.3%)
History of miscarriage	17258(2.8%)	748(2.4%)	18006(2.8%)	982(3.0%)	247(3.4%)	1491(3.3%)	492(3.0%)
History of induced abortion	75836(12.4%)	3507(11.3%)	79343(12.4%)	4059(12.4%)	905(12.6%)	6665(14.6%)	2284(14.1%)
History of birth defect	1638(0.3%)	40(0.1%)	1678(0.3%)	86(0.3%)	29(0.4%)	159(0.4%)	53(0.3%)
History of stillbirth	5019(0.8%)	209(0.7%)	5228(0.8%)	314(1.0%)	73(1.0%)	485(1.1%)	158(1.0%)
First pregnancy[♯]	395168(64.8%)	21038(67.9%)	416206(65.0%)	21516(65.9%)	4742(65.8%)	27287(60.0%)	10055(65.1%)
Primipara[♯]	44192(72.4%)	23292(75.1%)	464784(72.6%)	23963(73.4%)	5280(73.3%)	30819(67.7%)	11279(69.5%)
Pre-pregnancy physical examination							
Body mass index (kg/m^2)[♯]							
Underweight (<18.5)	124288(20.4%)	5515(17.8%)	129803(20.3%)	6876(21.1%)	1536(21.3%)	7496(16.5%)	2698(16.6%)
Normal (18.5-24.0)	405190(66.5%)	19824(63.9%)	425014(66.4%)	21319(65.3%)	4697(65.2%)	30406(66.8%)	10707(66.0%)
Overweight (24.0-28.0)	61389(10.1%)	4329(14.0%)	65718(10.3%)	3348(10.3%)	714(9.9%)	5672(12.5%)	2004(12.4%)
Obesity(≥28)	12395(2.0%)	1100(3.6%)	13495(2.1%)	751(2.3%)	176(2.4%)	1327(3.91%)	527(3.3%)
Lifestyle before pregnancy							
Active smoke[♯]	1471(0.2%)	79(0.3%)	1550(0.2%)	94(0.3%)	17(0.2%)	148(0.3%)	40(0.3%)
Passive smoke[♯]	104620(17.2%)	4757(15.4%)	109377(17.1%)	5990(18.4%)	1241(17.2%)	7725(17.0%)	2756(17.0%)

Husband smoke[♯]	164999(27.1%)	8947(28.9%)	173946(27.2%)	9270(28.4%)	2089(29.0%)	12462(27.4%)	4498(27.7%)
Alcohol[♯]	37912(6.2%)	1765(5.7%)	39677(6.2%)	2172(6.7%)	501(7.0%)	3281(7.2%)	1155(7.1%)
Lifestyle during early pregnancy							
Active smoke[♯]	3824(0.6%)	245(0.8%)	4069 (0.6%)	214(0.7%)	38(0.5%)	336(0.7%)	132(0.8%)
Husband smoke[♯]	124865(20.5%)	6270(20.2%)	131135(20.5%)	6453(19.8%)	1450(20.1%)	8862(19.5%)	3311(20.4%)
Alcohol[♯]	7226(1.2%)	401(1.3%)	7627(1.2%)	372(1.1%)	76(1.1%)	592(1.3%)	206(1.3%)

FSG: Fasting serum Glucose. IFG: impaired fasting glucose. PTB: preterm birth. LGA: large for gestational age.

[♯] Denominators provided as missing data existed.

[*] The distributions of pre-pregnancy status of FPG with respect to different baseline characteristics were all statistically (P<0.05), except for ethnicity.

Table 2. aRRs for PTB, LGA and severe LGA according to maternal pre-pregnancy IFG

	Events	Model 1[♯]		Model 2[┼]		Model 3[╪]	
		IRR(95%CI)	*P*	IRR(95%CI)	*P*	IRR(95%CI)	*P*
Preterm birth							
Normoglycaemia	30950(5.1%)	1.00(reference)	…	1.00(reference)	…	1.00(reference)	…
IFG	1690(5.5%)	1.07(1.02-1.12)	0.004	1.07(1.02-1.12)	0.008	1.07(1.02-1.12)	0.010
Early pretwem birth							
Normoglycaemia	6877 (1.1%)	1.00(reference)	…	1.00(reference)	…	1.00(reference)	…
IFG	324(1.0%)	0.93(0.83-1.04)	0.202	0.93(0.83-1.03)	0.175	0.92(0.83-1.03)	0.159
Large for gestational age							
Normoglycemia	43074(7.1%)	1.00(reference)	…	1.00(reference)	…	1.00(reference)	...
IFG	2458(7.9%)	1.12(1.04-1.20)	<0.001	1.12(1.07-1.16)	<0.001	1.10(1.06-1.14)	<0.001

Severe large for gestational age							
Normoglycaemia	15294(2.5%)	1.00(reference)	…	1.00(reference)	…	1.00(reference)	…
IFG	937(3.0%)	1.20(1.12-1.27)	<0.001	1.20(1.12-1.27)	<0.001	1.17(1.10-1.26)	<0.001

aRRs=adjusted risk ratios; PTB=preterm birth; LGA=large for gestational age, IFG=impaired fasting glucose.

♯ Model 1: risk ratios were adjusted for sociodemographic characteristics of maternal (age, education level, occupation, ethnicity, region and migrant population).

† Model 2: risk ratios were additionally adjusted for history of pregnancy (first gestation and primipara) and history of adverse pregnancy outcomes (preterm birth, miscarriage, induced abortion, birth defect, and stillbirth).

‡ Model 3: risk ratios were adjusted for pre-pregnancy body mass index, active smoking, passive smoking, husband smoking and alcohol consumption status of maternal before pregnancy and active smoking, husband smoking, alcohol drinking status during early stage of pregnancy, in additional to the covariates in Model 2.

Table 3. aRRs for impact of pre-pregnancy fasting glucose on PTB, LGA and severe LGA

Glucose categories	Total N (N with outcome)	Model 1♯		Model 2†		Model 3‡	
		IRR(95%CI)	*P*	IRR(95%CI)	*P*	IRR(95%CI)	*P*
PTB							
1	165897(8782)	1.00(reference)	…	1.00(reference)	…	1.00(reference)	…
2	144431(7164)	0.94(0.91-0.97)	<0.001	0.94(0.92-0.97)	<0.001	0.94(0.91-0.97)	<0.001
3	174513(8598)	0.93(0.90-0.96)	<0.001	0.93(0.91-0.96)	<0.001	0.93(0.90-0.96)	<0.001
4	93354(4748)	0.96(0.93-0.99)	0.015	0.96(0.93-0.99)	0.026	0.96(0.93-0.99)	0.022
5	36122(1936)	1.01(0.96-1.06)	0.788	1.00(0.96-1.05)	0.855	1.00(0.96-1.05)	0.904
6	19198(1032)	1.02(0.95-1.08)	0.634	1.01(0.95-1.08)	0.684	1.01(0.95-1.08)	0.736
7	6954(380)	1.03(0.93-1.14)	0.578	1.02(0.93-1.15)	0.635	1.02(0.92-1.12)	0.689
Per 1 SD	640469(32640)	0.99(0.98-1.00)	0.179	0.99(0.98-1.00)	0.177	0.99(0.98-1.00)	0.139
Early PTB							
1	165897(1901)	1.00(reference)	…	1.00(reference)	…	1.00(reference)	…

2	144431(1565)	0.95(0.89-1.02)	0.107	0.95(0.89-1.02)	0.129	0.95(0.89-1.01)	0.119
3	174513(1942)	0.97(0.91-1.04)	0.343	0.97(0.91-1.04)	0.394	0.97(0.91-1.04)	0.372
4	93354(1089)	1.02(0.94-1.09)	0.671	1.02(0.95-1.10)	0.631	1.02(0.94-1.09)	0.673
5	36122(442)	1.06(0.96-1.18)	0.244	1.06(0.96-1.18)	0.263	1.06(0.95-1.17)	0.282
6	19198(195)	0.89(0.77-1.03)	0.128	0.89(0.77-1.03)	0.120	0.89(0.77-1.03)	0.109
7	6954(67)	0.84(0.66-1.07)	0.166	0.84(0.66-1.07)	0.159	0.84(0.66-1.07)	0.147
Per 1 SD	640469(7201)	0.99(0.97-1.02)	0.638	0.99(0.97-1.02)	0.633	0.99(0.97-1.02)	0.583
LGA							
1	165897(10795)	1.00(reference)	…	1.00(reference)	…	1.00(reference)	...
2	144431(9860)	1.03(1.00-1.05)	0.043	1.02(1.00-1.05)	0.087	1.02(0.98-1.05)	0.154
3	174513(12616)	1.07(1.04-1.10)	<0.001	1.06(1.04-1.09)	<0.001	1.06(1.03-1.08)	<0.001
4	93354(7285)	1.14(1.11-1.17)	<0.001	1.14(1.10-1.17)	<0.001	1.12(1.09-1.16)	<0.001
5	36122(2922)	1.19(1.14-1.24)	<0.001	1.19(1.14-1.24)	<0.001	1.17(1.13-1.22)	<0.001
6	19198(1504)	1.16(1.10-1.22)	<0.001	1.16(1.10-1.23)	<0.001	1.14(1.08-1.20)	<0.001
7	6954(550)	1.18(1.08-1.27)	<0.001	1.18(1.09-1.28)	<0.001	1.15(1.06-1.25)	<0.001
Per 1 SD	640469(45532)	1.05(1.04-1.06)	<0.001	1.05(1.04-1.06)	<0.001	1.04(1.03-1.05)	0.001
Severe LGA							
1	165897(4018)	1.00(reference)	…	1.00(reference)	…	1.00(reference)	…
2	144431(3438)	0.97(0.93-1.01)	0.172	0.97(0.92-1.01)	0.149	0.96(0.92-1.01)	0.114
3	174513(4482)	1.03(0.99-1.08)	0.151	1.03(0.99-1.07)	0.193	1.02(0.98-1.07)	0.327
4	93354(2472)	1.05(1.00-1.11)	0.039	1.05(1.00-1.11)	0.040	1.04(0.99-1.10)	0.121
5	36122(1057)	1.17(1.10-1.25)	<0.001	1.17(1.10-1.25)	<0.001	1.15(1.08-1.23)	<0.001
6	19198(560)	1.17(1.07-1.28)	0.001	1.17(1.07-1.28)	0.001	1.14(1.05-1.25)	<0.001

7	6954(204)	1.18(1.03-1.35)	0.029	1.18(1.03-1.36)	0.026	1.15(1.01-1.32)	0.024
Per 1 SD	640469(16231)	1.03(1.02-1.05)	<0.001	1.03(1.02-1.05)	<0.001	1.03(1.01-1.04)	<0.001

aRRs= adjusted risk ratios; PTB=preterm birth; LGA=large for gestational age.

Fasting glucose categories are defined as follows: category 1: less than 4.3mmol/L; category 2: 4.3-4.7mmol/L; category 3: 4.7-5.2mmol/L; category 4: 5.2-5.6mmol/L; category 5: 5.6-6.2mmol/L; category 6: 6.2-6.7mmol/L; category 7: 6.7-7.0mmol/L.

♯ Model 1: risk ratios were adjusted for sociodemographic characteristics of maternal (age, education level, occupation, ethnicity,

┼ Model 2: risk ratios were additionally adjusted for history of pregnancy (first gestation and primipara) and history of adverse pregnancy outcomes (preterm birth, miscarriage, induced abortion, birth defect, and stillbirth).

╪ Model 3: risk ratios were adjusted for pre-pregnancy body mass index, active smoking, passive smoking, husband smoking and alcohol consumption status of maternal before pregnancy and active smoking, husband smoking, alcohol drinking status during early stage of pregnancy, in additional to the covariates in Model 2.

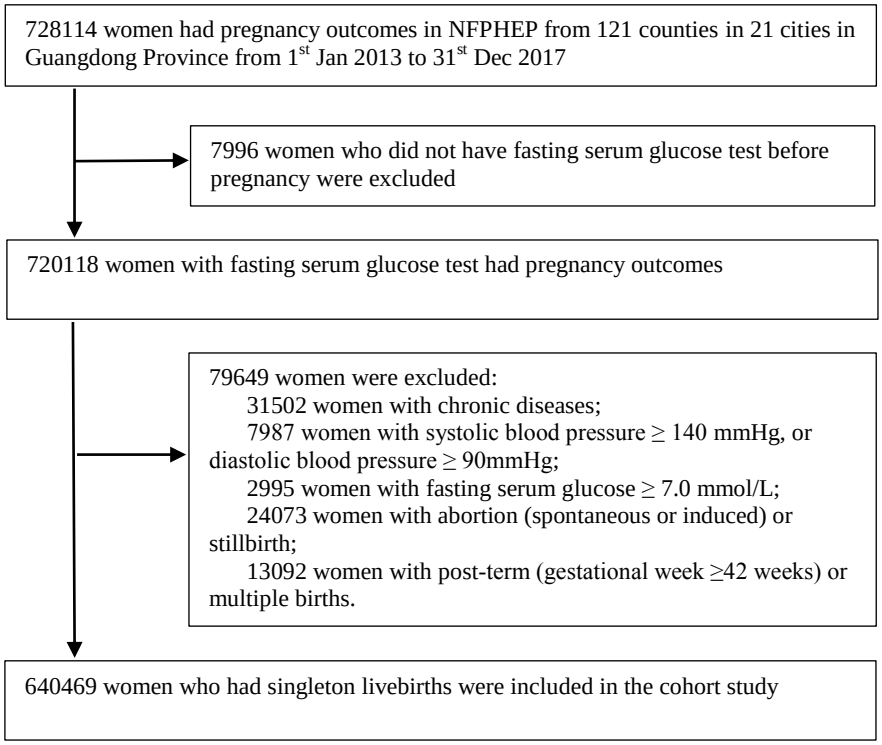

Figure 1 Selection of Participants