Differences in Incidence and Risk Factors of Infertility Between Couples Who Desire a First and Second Child: A Prospective Cohort Study

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Research Article

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Abstract

Background: With the implementation of the two-child policy in China, more couples expressed their desire to have a child. We conducted this study to evaluate the incidence and risk factors of infertility in couples intending to have a first child and second child.

Methods: Couples who presented to the pre-pregnancy clinical centers were enrolled from 2013 to 2017. Participants were categorized into “first child intention” and “second child intention” groups based on the number of children they already had. Couples were followed up every three months until pregnancy or 12 months. Data regarding the sociodemographic characteristics, history of reproduction and gynecology, history of male disease, and laboratory and imaging examination results were collected. Odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were calculated and adjusted for potential confounding factors.

Results: The overall infertility incidence was 16.95% (369/2177). The infertility incidence of “first child intention” and “second child intention” was 19.30% (355/1839) and 4.14% (14/338). The study showed great differences in infertility risk factors between two groups. Risk factors for “first child intention” infertility included advanced age (>35 years), abnormal body mass index (BMI), longer menstrual durations, endometrial polyps, polycystic ovarian syndrome (PCOS), salpingostomy, and history of mycoplasma. However, in “second child intention” group, clinical risk factor was slightly different, such as leiomyoma, higher age (>40 years).

Conclusion: The incidence and risk factors of infertility are significantly different between “first child intention” group and “second child intention” group. Early and targeted intervention for couples in different groups at high risk can help reduce infertility and social burden.

Plain English Summary

Infertility is defined as the failure of pregnancy after at least 12 months of unprotected regular sexual intercourse. Few researchers have investigated the infertility rate in Shanghai in the past 15 years. Up to now, far too little attention has been paid to the infertility of couples intending a second child.

We performed a prospective cohort study in Shanghai to evaluate incidence and risk factors of infertility in the couples intending a first or second child. The investigator will conduct a questionnaire survey on the participants and follow them for one year

Finally, 1839 couples with first child intention, 338 couples with second child intention included in this study. The overall infertility incidence was 16.95% (369/2177). The infertility incidence of “first child intention” and “second child intention” was 19.30% (355/1839) and 4.14% (14/338). Risk factors for “first child intention” infertility included advanced age (>35 years), abnormal body mass index (BMI), longer menstrual durations, endometrial polyps, polycystic ovarian syndrome (PCOS), salpingostomy, and

history of mycoplasma. And in “second child intention” group, clinical risk factor was slightly different, such as leiomyoma, higher age (>40 years).

Since studies have shown that there are large differences in the risk factors of infertility between the two groups, early and targeted intervention for couples in different groups at high risk can help reduce infertility and social burden.

Background

As a common medical problem, factors influencing fertility have not been elucidated [1]. Previous studies found that reproductive system diseases, social and psychological factors contribute to infertility [2, 3]. Additionally, due to differences such as region, environment, and economy, the incidence of infertility varies significantly around the world [4, 5].

Previous studies have indicated that 12-month infertility rates were 15.6% (2009-2010) and 10.5% (2007) in Canada and Scotland, respectively [6, 7]. And the overall prevalence of infertility in Iran was 8% in 2006 [8]. A survey performed in China involving 17,275 women from 8 provinces in 2007 estimated that the overall infertility rate was 15.6% [9]. And the infertility rate in Shanghai was 9% in 2002 [10]. However, these results were based on data that are now outdated, and the current infertility rate in Shanghai is unknown.

Infertility is a national concern that causes emotional, financial, and societal burdens [11]. Surveys have shown that the financial burden of infertility in China in 2008 was estimated to be 11.4 billion to 32.5 billion dollars [12]. Infertility rates have continued to increase in the Chinese population, from 6.7% in 2005 to 15.5% in 2018. 9 As the incidence of infertility increases, so does its societal burden. As of the end of 2018, there were 497 assisted reproductive technology (ART) centers approved by China government. According to statistics, the total number of human ART cycles per year has exceeded 1 million, and the number of babies born has exceeded 300,000 [13]. Therefore, infertility deserves more attention so that this problem can be solved urgently.

Existing studies recognize that infertility can have different definitions according to different classifications. It can be divided into primary infertility and secondary infertility (according to pregnancy history), temporary infertility and permanent infertility (according to the duration), physiological infertility and pathological infertility (according to the cause of infertility) [14, 15, 16]. At present, there is no clear definition of infertility of the couples who intend to have a first child or second child.

Since China implemented the second child policy, it is estimated that about 90 million targeted women have been allowed to have a second child [17]. Moreover, recent evidence showed that an estimated 60% are over 35 and a half over 40 among 90 million women [18]. Compared with primigravids, increasing age and other potential factors would bring challenges to the fertility of women who intend to have a second child. Recent researches have focused on the prevalence and the risk factors for primary infertility and secondary infertility [14, 19]. Up to now, far too little attention has been paid to the infertility of couples

intending a second child. Based on few researchers who have investigated the incidence of infertility in Shanghai in the past 15 years, we performed a prospective cohort study in Shanghai to evaluate incidence and risk factors of infertility in the couples intending a first or second child.

Materials And Methods

Study Design And Participants

We performed a single-center, prospective cohort study in pre-pregnancy centers of in Shanghai, China from January 2013 to December 2017. Unlike the cross-sectional studies that most studies do, we conduct a prospective cohort study to reduce the deviation of recall. Since 2012, China have carried out pre-pregnancy check-ups, prompting community-based couples to become pregnant to seek services from designated institutions [20]. As a designated institution, the pre-pregnancy center provides pre-pregnancy education, consultation and ordinary examinations (including infectious diseases and reproductive system examination for women) for childbearing age couples in surrounding communities. Our pre-pregnancy centers cover the main urban areas in southern Shanghai. Under these circumstances, the objective of this study was to evaluate the incidence of and risk factors for infertility in couples planning to conceive.

The inclusion criteria were couples of reproductive ages (20 to 49 years of age) who presented to the pre-pregnancy clinic center with the intention of becoming pregnant and regular sexual activity. Participants with extreme values (body mass index [BMI] <17 or >33 kg/m2) or history of infertility, or those who were not planning to become pregnant, or those whose laboratory findings did not allow them to be pregnant within the next year, or those who planned to have a third child or more were excluded. Written informed consent was obtained from all participants.

Definition Of Infertility

According to the World Health Organization (WHO) definition, infertility is the failure of pregnancy after at least 12 months of unprotected regular sexual intercourse [21]. Primary infertility is defined as infertile couples with no history of pregnancy, while secondary infertility is defined as infertile couples with a history of pregnancy [19]. The prevalence of infertility can be changed with different approaches. The primary infertility was commonly calculated by the DHS-type (Demographic and Health Survey) infertility measure [22]. In addition, some scholars have applied the novel current duration approach, and calculated that the prevalence of infertility was twofold higher than use the traditional constructed measure [23]. These studies emphasize the importance of definition and methodological methods in estimating the prevalence of infertility.

In our study, “infertility of first child intention” refer to the fact that the couples who intend to have a first child, with the inability to become pregnant for at least 12 months of regular sexual activity. Similarly, “infertility of second child intention” was defined as the infertility of couples who already had first child

and wished to have a second child. Different from secondary infertility, “infertility of second child intention” is aimed at the couples with previous successful delivery, and does not include the outcome of the previous pregnancy for abortion and ectopic pregnancy.

Procedures

Based on inclusion and exclusion criteria, proportionate sampling was used to select the study participants. The information collected for each participant included sociodemographic characteristics (e.g., age, marital status, education, occupation, individual annual income, smoking status), history of reproduction and gynecology (e.g., number of pregnancies, pregnancy outcomes, age at menarche, menstrual cycle, menstrual duration, menstrual blood volume, medical history, operative history), disease history of the male spouse (e.g., medical history, operative history), and pre-pregnancy medical examination results (e.g., serological antibody, pelvic ultrasound).

To ensure a high quality of data collection, the questionnaire was filled out by the investigator during interview according to standard protocol. If participants did not answer any question because they were unwilling to respond, then we treated that as missing information. Follow-up was performed by a well-trained investigator via telephone every three months until delivery or 12 months.

Based on whether participants were infertile, couples with first child intention were then deemed to “infertility of first child intention” group and “fertility of first child intention” group. During the same study period, couples with second child intention were deemed to “infertility of second child intention” group and “fertility of second child intention” group. According to the definition of infertility, the incidence of infertility was calculated as: the number of infertile women represent the numerator and the number of women intending to get pregnant represent the denominator.

Statistical analysis

Based on a previous pilot study, we assumed that the prevalence of infertility among couples was 15%. With an allowable error of 2% and two-sided 95% confidence interval (CI), a total sample size of 1273 was required. To minimize the sampling error, we calculated a final sample size that was 1.5-fold the previous one, resulting in a total sample size of 2000. With the calculation, at least 2000 couples should be asked join at the baseline. During the recruitment process, study sample were employed with probability proportionate. From 2013 to 2017, couples who presented pre-pregnancy center was the source population for the cohort. A random sampling of one-fifteenth of them was used. Finally, a total of 2300 couples were enrolled.

Infertility was treated as a binary outcome, and corresponding 95% CIs were calculated assuming a binomial distribution of the observed number of events. Univariable conditional logistic regression analysis was also used to calculated crude odds ratios (ORs) and their 95% CIs. Multivariable logistic regression analysis was performed to explore the potential risk factors and corresponding ORs. Before

the logistic regression model construction, the multi-collinearity analysis was made between independent variables included in the regression models. We chose the covariates examined by multivariable logistic regression based on their clinical relevance and previously established associations with infertility. All statistical analysis was performed using IBM SPSS Version 21.0 (IBM Corp., Armonk, NY, USA). All p values were estimated using two-sided tests, and the differences were considered statistically significant when $p < 0.05$.

Results

In our study, from January 2013 to December 2017, 2300 couples in the cohort were selected from 34,034 visits to pre-pregnancy center based on a ratio of 15:1; However, 48 (2.09%) couples who were worried about disclosing their private information refused to participate in the investigation; 64 (2.78%) were lost to follow-up. Finally, 1839 couples with first child intention, 338 couples with second child intention included in this study (the recruitment flow chart is shown in Fig. 1).

Among all couples who plan to conceive (n=2177, the overall incidence of infertility was 16.95% (95% CI, 15.37%-18.53%; infertility=369, fertility=1803). The incidence of “infertility of first child intention” was 19.30% (95% CI, 17.50%-21.11%; infertility=355, fertility=1484). By contrast, the incidence of “infertility of second child intention” was 4.14% (95% CI, 2.01%-6.28%; infertility=14, fertility=324).

Baseline Characteristics

Table 1 shows the differences in the sociodemographic and socioeconomic characteristics of couples in this study. The mean (±standard deviation [SD]) age was 29.76 (±3.71) years for overall women and 31.36 (±4.39) years for overall men. Among couples with “first child intention”, the mean (±SD) age was 29.50 (±3.52) for women and 31.12 (±4.22) for men. Among couples with “second child intention”, the female and male mean (±SD) age was 31.11 (±4.36) and 32.53 (±4.97). Furthermore, the mean BMI (±SD) values for overall women and men were 21.08 (±2.69) kg/m2 and 23.67 (±2.82) kg/m2, respectively. Among couples with “first child intention”, the mean BMI (±SD) was 21.07 (±2.70) kg/m2 for women and 23.71 (±2.87) kg/m2 for men. Among couples with “second child intention”, the mean BMI (±SD) was 21.15 (±2.60) kg/m2 for women and 23.52 (±2.59) kg/m2 for men. Most women and men completed junior college or university or above. More than 90% of women were employed. And the largest percentage of households had annual incomes of more than 20,000 yuan.

In the “couples with first child intention” group, the proportions of both women and men with older age, higher BMI and lower incomes was significantly greater in the infertility group than in the fertility groups. Furthermore, women with low education were more likely to be infertility in this group. In the “couples with second child intention” group, the proportions of women with older age, low education and man with low education was significantly greater in the infertility group than in the fertility groups.

Univariate Analysis

Figure 2 shows the crude unadjusted ORs and their 95% CIs for the association between infertility and female medical history in two groups. In the “couples with first child intention” group, compared with women who had normal menstruation, women with longer menstrual cycles, longer menstrual durations were more likely to be infertile. Regarding the medical history, the occurrence of infertility was associated with factors such as leiomyoma, ovarian cysts, endometrial polyps, endometriosis, polycystic ovarian syndrome (PCOS), history of lower genital tract infection (mycoplasma, chlamydia and condyloma acuminate). Moreover, among infertile couples, a high proportion of women had a history of surgery such as uterine myomectomy, salpingostomy, transcervical polyp resection, and hysteroscopic adhesiolysis, which were associated with a significantly higher risk of infertility. In terms of “couples with second child intention” group, the crude OR of infertility among women with later menarche and history of leiomyoma was significantly lower than that of women who did not.

Regarding the male history of disease (Table 2), prostatitis, lower genital tract infection (mycoplasma and chlamydia) were factors that could lead to infertility in the “first child intention” group. However, no significant differences were found in male history in “second child intention” group between infertility and fertility.

Multivariate Analysis Of Risk Factors For Infertility

Table 3 presents the results of the multivariate analysis of the risk of infertility. For couples intending to have first child, high BMI (≥24 kg/m2) and older age (>35 years) for women and low BMI (<18.5 kg/m2) for men were found to be risk factors for infertility. As for female menstrual history, the results indicated that women with longer menstrual durations (OR, 4.47; 95% CI, 2.25-8.88) were at a greater risk for infertility. Moreover, women with a history of endometrial polyps (OR, 2.52; 95% CI, 1.28-4.97), or PCOS (OR, 6.72; 95% CI, 1.79-7.39), or endometriosis (OR, 2.52; 95% CI, 1.27-4.97), or mycoplasma infection in the lower genital tract (OR, 1.54; 95% CI, 1.09-2.40) were more likely to experience infertility than women who did not. Correspondingly, previous salpingostomy (OR, 3.44; 95% CI, 1.68-7.07) was also associated with a higher risk of infertility.

Turning now to “second-child intention” group, the ORs were not significant among women with age range from 35-39; however, the ORs become significant when female age over 40 (OR, 7.36, 95% CI: 1.01–53.84). Surprisingly, female history of leiomyoma (OR, 5.60; 95% CI, 1.06-29.76) was significant risk factors of infertility in “couples with second child intention” group, while this factor is not significantly different in “couples with first child intention” group (OR, 1.38; 95% CI, 0.92-2.07). Furthermore, women who had experienced infertility were more likely to have history of endometriosis (OR, 38.68; 95% CI, 1.16-1286.82).

Discussion

The overall incidence of infertility among was 16.95% in Shanghai. Our study presented the incidence of “first child intention” and “second child intention” infertility was 19.30% and 4.14%, respectively. To our knowledge, this is the first study analyzing the infertility incidence and risk factors in couples with “first child intention” and “second child intention”. As can be seen from the above infertility rate, the infertility incidence of “second child intention” is significantly lower than that of “first child intention”, which means that the contribution of the overall infertility incidence is mainly for the couples with “first child intention”. There are two possible reasons: first, the focus of our study was on the incidence of infertility rather than the prevalence of infertility. Therefore, we excluded patients with previous infertility history at the time of inclusion. Second, our study also showed great differences in infertility risk factors between two groups. As for couples with “first child intention”, obesity (BMI ≥24 kg/m2), advanced age (>30 years old), female gynecological diseases such as endometrial polyps, PCOS, endometriosis, mycoplasma infection of the lower reproductive tract, and previous surgical history of tubal infertility were associated with infertility. Among couples with “second child intention”, only the following variables were significantly related to infertility: age over 40, leiomyoma and lower education levels.

Age is recognized as one of the causes of infertility [24]. The incidence of infertility in Shanghai today is almost doubled that of 2002, which is also higher than the incidence of infertility in China [25]. The result might be related to the social, cultural and economic development of Shanghai in the past 15 years [5]. Economic development has brought about tremendous social progress, and has also stimulated people's pursuit of education, career and income, which causes some of couples to miss the best time to conceive. Previous studies have suggested that the best age for women to pregnancy is before 35 years [26]. As age increases for females, ovarian function declines and fertility is naturally reduced [27]. Not only that, the incidence of some gynecological diseases would also increase with the increase of age. The 2002 Shanghai infertility rate survey showed that women over the age of 30 accounted for only 38.28%, but now it accounted for 43.64%. This ratio was also higher than the 30.07% obtained in the 2015 survey of seven major cities in China.

In our study, among women intending to have a first child, age range from 35-39 was associated with a higher risk of infertility. While in the “second child intention” group, age range from 35-39 was no longer a risk factor for infertility until reaching 40 or older. This finding has not been reported in previous studies. There could be three major reasons for this contradiction: (1) women with “second child intention” experienced a successful pregnancy, which suggests that these couples have a complete chain from the production of eggs and sperm to the success of pregnancy; (2) women with advanced age are less likely to develop new ovulatory dysfunction [28]. (3) although the fertility of women began to decline after the age of 35, complete loss of fertility often occurs after the age of 40 [29, 30], with a significantly increased risk of infertility. The results suggest some implications for clinicians: more health improvement strategies should be carried out in pregnancies over 40 years for women with “second child intention” and over 35 years for women with first child intention. In terms of male age, the advanced age of men with “first child intention” also had a significant relationship with infertility. However, due to relatively limited sample size, this study did not find a certain correlation between old age and infertility in male “second child intention” group.

Numerous studies have shown the effects of the female reproductive history and gynecological history on infertility [31, 32]. Our investigation confirmed that factors related to infertility for women included menstrual history (long menstrual cycle, or long menstrual duration), gynecological history (leiomyoma, PCOS, endometrial polyps, or endometriosis), surgical history (salpingostomy), and infection history (chlamydia). Several researchers have explained the relationship between these risk factors and infertility, which may be related to ovulation disorders, deterioration of the intrauterine environment, and pathological changes in the cervix [33, 34].

Since the implementation of China's second child policy, several reports have shown an increase in the intention of having a second child among women [35, 36]. However, the number of newborns in China has declined in recent years, especially in economically developed cities like Shanghai. According to statistics, there are 19 authorized ART centers in Shanghai, which could provide assisted reproductive technologies including in vitro fertilization and embryo transfer (IVF-ET), artificial insemination, intracytoplasmic sperm injection (ICSI) and preimplantation Genetic Diagnosis (PGD). Although infertile couples may seek comprehensive treatment services through medical institutions in Shanghai, it is still a huge cost to both the patients and the government. To some extent, our findings could guide the government and medical institutions to make targeted investments in the risk factors of infertility, in order to reduce the economic burden on infertility treatment.

Our study had some limitations. First, due to the lack of male information, there are no significant risk factors related to male infertility. Second, we choose probability proportionate rather than PPS (Probability Proportional to Size) technique when recruiting participants. As proportional sampling methods, both methods are effective sampling methods to obtain representative populations [37]. However, PPS should be used in this study as a more reasonable sample selection method. We would take a more appropriate sample size selection method in the future study. Finally, based on our analysis of the infertility incidence, not the infertility prevalence, the study excluded infertile people at the inclusion stage. In the future, we will conduct the cross-sectional studies to study the prevalence of infertility between couples with “first child intention” and “second child intention”.

Conclusions

This survey showed that among those who present to our pre-pregnancy clinical, the infertility rate is approximately 17.09%, which is significantly higher than that of other provinces in China during the same period. This is likely related to the economy, environmental quality of Shanghai, and psychological pressure of those who work there. The incidence of “first child intention” and “second child intention” infertility was 19.30% and 4.14%, respectively. For couples with “first child intention”, it could be inferred that the risk factors for infertility are age (women), BMI (women and men), menstrual duration, education (women), history of PCOS, endometriosis and endometrial polyps, tubal surgery, and history of chlamydia. By contrast, risk factors for infertility in couples with “second child intention” are female age, leiomyoma and endometriosis. The social and economic burdens of infertility will increase as the number

of infertile individuals increases. Consequently, in the future, we need to identify more risk factors for infertility and target medical resources to different groups of infertility patients.

Abbreviations

ORs
Odds ratios
CIs
confidence intervals
BMI
abnormal body mass index
PCOS
polycystic ovarian syndrome
ART
assisted reproductive technology
WHO
World Health Organization
DHS-type
Demographic and Health Survey
SD
standard deviation
IVF-ET
in vitro fertilization and embryo transfer
ICSI
intracytoplasmic sperm injection
PGD
preimplantation Genetic Diagnosis
PPS
Probability Proportional to Size.

Declarations

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Authors' contributions

Jian Zhang. and Luting Chen were conceived of the study and participated in its design, as well as supervised the study and critically revised the manuscript. Chenfeng Zhu performed the investigation and

wrote the manuscript. Li Yan and Jiahao Wu contributed to collection. Yang Wang and Chuqing He participated in statistical analysis. All authors read and approved the final version of the manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Ethics approval and consent to participate

This study was approved by the institutional review board (GKLW201519, obtained in June 2012) of the International Peace Maternity and Child Health Hospital (IPMCH, Shanghai, China). Written informed consent was obtained from each subject before recruitment. The patient's right to refuse to participate in research and quit the study at any time was guaranteed, and all participant information was kept confidential.

Consent for publication

Not applicable.

Competing interests

The authors declare there is no conflict of interest.

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Tables

Due to technical limitations, tables 1 to 3 are only available as a download in the Supplemental Files section.

Figures

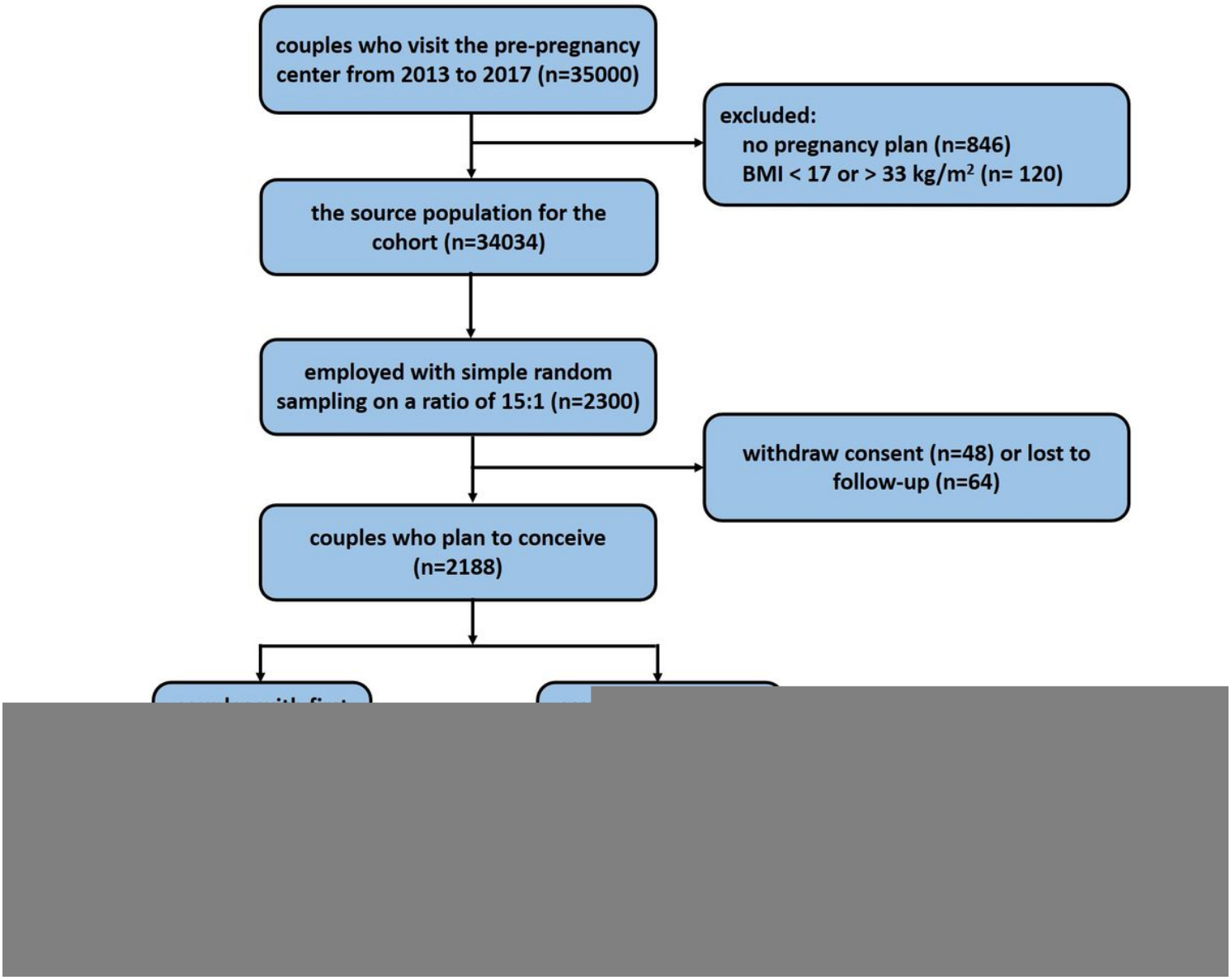

Figure 1

Recruitment profile of the study.

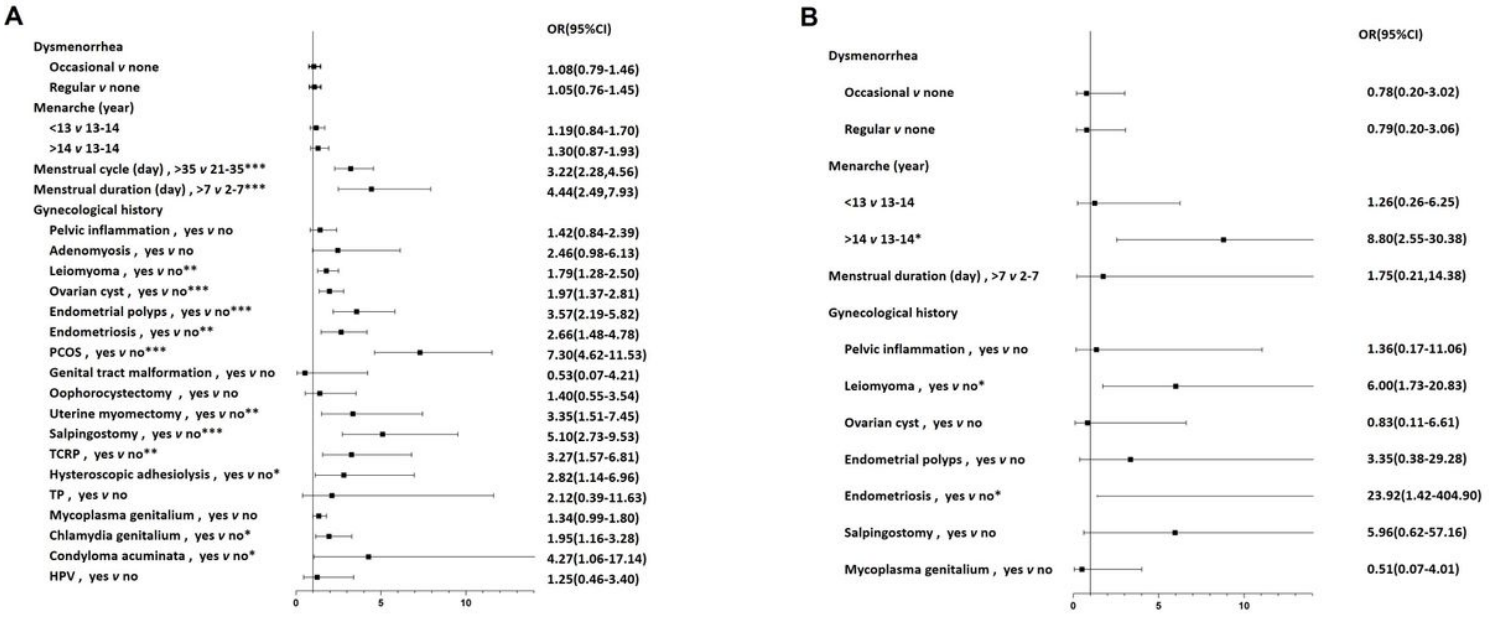

Figure 2

Forest plot of the medical history of women with first or second child intention. (A) represent the medical history of women with first child intention. (B) represent the medical history of women with second child intention.

*: P<0.05; **: P<0.01; ***: P<10-3

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1Demographiccharacteristic.xlsx
- Table2Medicalhistoryofmen.xlsx
- Table3Multivariablelogisticregressionanalysis.xlsx
- Supplementarytable1Multicollinearityanalysis.xlsx