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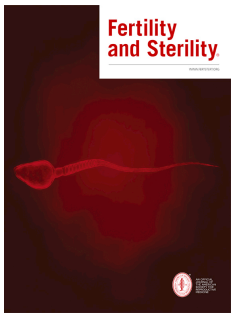

Inverse association of pre-pregnancy Systolic Blood Pressure and Live Birth Rate in normotensive women undergoing IVF/ICSI

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Running Title: Blood Pressure and IVF/ICSI Outcomes.

Inverse association of pre-pregnancy Systolic Blood Pressure and Live Birth Rate in normotensive women undergoing IVF/ICSI

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Attestation Statement:

• Data regarding any of the subjects in the study has not been previously published unless specified.

• Data will be made available to the editors of the journal for review or query upon request.

Data Sharing Statement: The study protocol, dataset, and statistical code can be made available by request to the corresponding author. Access will require submission of a protocol, approval by our review committee, and the signing of a data access agreement. Potential access will be for the period beginning 3 months and ending 5 years following article publication.

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Trial registration: NA.

Capsule: An increase of systolic blood pressure is negatively associated with live birth rate after IVF/ICSI in normotensive women (RR per 10mmHg = 0.988, 95%CI, 0.981 - 0.995, *P* =0.001).

Structured Abstract

Objective: To explore whether maternal baseline systolic and diastolic blood pressure (SBP and DBP) affect pregnancy outcomes particularly in normotensive women (SBP within 90-139 mmHg, DBP within 60-89 mmHg) but also hypertensive women undergoing in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI).

Design: Retrospective cohort study.

Subjects: The study included 73,462 patients who underwent IVF/ICSI at the Reproductive and Genetic Hospital of CITIC-Xiangya between January 1, 2016, and November 30, 2020, selected based on pre-established criteria. Analysis was limited to the first transfer cycle of the first stimulation cycle.

Exposure: Baseline SBP and DBP.

Main Outcome Measures: Primary outcome focused on the live birth rate (LBR), with secondary outcomes including clinical pregnancy rate, ectopic pregnancy rate, first trimester miscarriage rate, 2nd or 3rd trimester fetal loss, and delivery/neonatal/maternal outcomes. Analytical methods included Poisson regression, linear regression, linear mixed-effect model, and restricted cubic spline analysis as appropriate.

Results: For normotensive women, a 10mmHg increase in SBP was associated with an adjusted relative risk (aRR) of 0.988 (95% CI: 0.981-0.995, *P*=0.001) for live birth likelihood. DBP, however, was not significantly

associated with LBR after adjustments. Secondary outcomes indicated that increases in SBP and DBP were associated with higher risks of first trimester miscarriage, gestational diabetes mellitus, and gestational hypertension in the normotensive subset. Sensitivity analyses confirmed these associations between SBP/DBP and LBR, consistent with the main findings even under stricter guidelines and after adjusting for multiple confounders. Subgroup analyses showed variation in the impact of blood pressure on LBR across different demographics and conditions. Consistent with earlier studies on blood pressure and birth outcomes, we found a 5.4% (aRR per 10mmHg =0.946, 95%CI: 0.907-0.986, *P* =0.009) reduction of LBR in the hypertensive subgroup. **Conclusion:** SBP impacted LBR outcomes in normotensive women undergoing IVF/ICSI, might suggest the need for reconsidering blood pressure management guidelines for reproductive-aged women, focusing on reproductive health in addition to cardiovascular risk.

Keywords: maternal blood pressure, live birth rate, first trimester miscarriage rate, IVF/ICSI.

INTRODUCTION

The live birth rate (LBR) following in vitro fertilization (IVF) / intracytoplasmic sperm injection (ICSI) is a pivotal clinical outcome parameter from the patient's perspective (1). Couples grappling with fertility challenges and seeking assistance from an assisted reproductive technology (ART) center primarily aspire to achieve a healthy baby. Since the inception of ART as a therapeutic option for these patients about three decades ago, scientists have been continuously engaged in comprehending and optimizing the factors influencing the success rate (2). Various clinical factors, including maternal age (more precisely, age of the oocyte), poor ovarian reserve, hydrosalpinx, tobacco or substance abuse, leiomyoma, endometriosis, prior pregnancy history, unsuccessful IVF cycles, obesity, endometrial thickness, and female height (3–6), have been described in many studies as independent determinants of LBR after ART. Many of these factors, such as maternal age, cannot be influenced or improved by treatment. This partly accounts for the relatively sluggish progress in improving the LBR after ART over the past decade. Pre-existing hypertension in women undergoing ART treatment is indeed a relatively rare but potentially modifiable risk factor for adverse pregnancy outcomes (7). Diagnostic criteria for hypertension in this population are not based on studies involving women undergoing ART, they align with the blood pressure criteria in the general population (8). Reproductive health is as of today not considered in the blood pressure guidelines for the general population,

however, blood pressure targets might be different in young women receiving ART treatment.

Our very recent post-hoc analysis of an earlier observational study (9,10) focusing initially on the effects of vitamin D, we saw that high normal blood pressure was associated with a lower LBR in young women undergoing fresh embryo transfer. Given the substantial clinical importance of this finding for reproductive medicine and recognizing the limitations of the above-mentioned pilot study (including study size and exclusion of key subgroups like women with abnormal uterine anatomy, endometriosis, intrauterine adhesions, untreated hydrosalpinx, etc.), we have now conducted a comprehensive study involving over 70,000 women undergoing their initial IVF/ICSI cycle. This study analyzed the impact of variations within the normal blood pressure range, as defined by current hypertension guidelines, on LBR and other assisted reproductive outcomes. To enable a comparison of variations in the normal blood pressure range with the known negative effects of hypertension on pregnancy outcomes, hypertensive women were also examined before initiation of IVF/ICSI therapy.

Materials and Methods

The study was approved by the Ethics Committee of the Reproductive and Genetic Hospital of CITIC-Xiangya, Changsha, China (approval number: LLSC2023001), and followed the Strengthening the Reporting of Observational Studies in Epidemiology

reporting guideline. More details of this section are presented in the Supplemental study protocol.

Design, setting and exposure

This was a retrospective cohort study of women who underwent IVF/ICSI treatment at the Reproductive and Genetic Hospital of CITIC-Xiangya from January 1st, 2016 to November 30th, 2020. Inclusion criteria were women aged 20-45 years, with autologous oocytes, the first transfer cycle under the first stimulation cycle in the hospital, and the interval between the date of blood pressure measurement and the date of embryo transfer was no more than 6 months. The blood pressure was measured when determining the ovulation stimulation regimen. Trained nurses conducted three blood pressure measurements using an automatic blood pressure measuring system (Mibobo, Shenzhen Raycome Health Technology Co., Ltd. Shenzhen, China) with 5-minute breaks between measurements, the measurement requirements was as described before (9). The mean values were calculated and used in the analyses. Hypertension was defined as SBP ≥140 mmHg or DBP ≥90 mmHg according to the 2020 International Society of Hypertension (ISH) global hypertension practice guidelines (11). Women with missing blood pressure values, SBP below 90 mmHg or DBP below 60 mmHg were excluded.

Primary and secondary outcomes

The primary outcome was live birth resulting from the embryo transfer, defined as one or more living infants of any gestational age. Multiple births counted as one live-birth

delivery. The secondary outcomes were clinical pregnancy (defined as one or more gestational sacs with fetal heart activity under ultrasonography 4 weeks after embryo transfer), good birth outcome (defined as live birth after 37 weeks of gestation, with a birth weight between 2500 and 4000 g and without major congenital anomalies) (12), ectopic pregnancy, first trimester miscarriage (defined as intrauterine pregnancy loss after confirmation of gestational sacs during the first trimester), 2nd or 3rd trimester fetal loss (defined as the loss of an intrauterine pregnancy during the second or third trimester), gestational diabetes mellitus (GDM), gestational hypertension, preterm birth (<37 weeks of gestation), neonatal malformation, gestational weeks at delivery, birth weight and Z-score , which was defined as ((infant birthweight - mean birthweight at the same gestational age for the same gender in the reference population) / standard deviation of birthweight at the same gestational age for the same gender in the reference population) (13,14).

Statistical analysis

This study divided participants into three groups based on the International Society of Hypertension criteria: normotensive (SBP 90-139 mmHg, DBP 60-89 mmHg), hypertensive (SBP ≥140 mmHg or DBP≥90 mmHg), and those receiving anti-hypertensive treatment (11). Participant demographics, baseline clinical characteristics, oocyte retrieval and embryo transfer details for each group were shown and compared with respect to live births. Data was presented as mean ± standard deviation, or frequency (%), fitting the data distribution. The normality of continuous

variables was verified using the Kolmogorov-Smirnov test. Differences between groups were determined using the two-sample t-test, Kruskal-Wallis test, or Pearson's Chi-square test, as appropriate.

Restricted cubic spline (RCS) regression models were used to explore the dose-response relationships between blood pressure and outcomes (15). Due to limited sample size in the anti-hypertensive treatment group, the impact of various blood pressure measures (SBP, DBP and mean arterial blood pressure) on the primary outcome (LBR) was just assessed in normotensive and hypertensive groups. Of which, only the primary outcomes were evaluated among the hypertensive group, secondary outcomes were confined to the normotensive group and focused solely on SBP and DBP. All blood pressure values were separately included in the analyses as continuous variables, with their distributions displayed in histograms. The RCS models were optimized for accuracy and overfitting using the Akaike information criterion. Generalized additive models were used to fit the curves for the crude probability of live birth, while generalized linear models, adjusted for potential confounders, evaluated relative risks (RRs), setting the 10th percentile as reference values.

To assess the impact of blood pressure variations (per 10 mmHg) on reproductive outcomes in the normotensive group, we employed multivariate Poisson regression, linear regression, and linear mixed-effect models. The model choice was based on the dependent variable's data type. All the multivariate statistical analyses were adjusted for female age, infertility type, body mass index (BMI), antral follicle count (AFC), anti-

Müllerian hormone (AMH), untreated hydrosalpinx, leiomyoma, endometriosis, endometrial thickness, transfer type and high-quality embryo transfer, in line with published studies (16–20). Estimated RRs and β coefficients were reported with 95% confidence intervals (CIs).

Sensitivity analyses, adhering to stricter American College of Cardiology (ACC)/ American Heart Association (AHA) guidelines (21), redefined normal blood pressure (SBP 90-129 mmHg, DBP 60-79 mmHg) and assessed the impact of blood pressure(per 10 mmHg) on LBR in this normotensive subset. Some of the adjusted variables in the main analysis were linked to live birth outcomes but not directly to blood pressure. Consequently, not all of these variables qualify as true confounders (22). To address this, building upon the foundation established by incorporating covariates identified from prior research, we further refined our analysis through sensitivity analyses. Based on the initial normotensive dataset defined as the ISH guideline, we implemented two additional strategies to refine our confounder selection and verify the stability of our results. The first strategy involved conducting single-factor analysis to identify baseline variables significantly correlated with both blood pressure and LBR. The second strategy employed LASSO regression, coupled with 10-fold cross-validation, to accurately identify critical variables. Multicollinearity was considered in all variable selection processes. Prespecified subgroup analyses explored the association between blood pressure and outcomes across various demographics and clinical characteristics including female age, BMI, infertility type,

cycle type, ART type, endometrial thickness, and infertility factors. All statistical tests were two-sided, with P<0.05 considered significant. Analyses were conducted using R version 4.3.2.

RESULTS

Basic characteristics

From January 1, 2016, to November 30, 2020, the Reproductive and Genetic Hospital of CITIC-Xiangya completed 148,658 transfer cycles for 104,721 patients. Following the pre-established criteria, 73,462 transfer cycles were included in the overall analysis (Figure 1). Of these, 70,545 were normotensive,2544 met diagnostic criteria for hypertension, and 373 were undergoing anti-hypertensive treatment. We detailed participant demographics, clinical characteristics, oocyte retrieval, and embryo transfer cycle information for each group in Supplemental table 1 and 2. The data revealed that younger patients were more likely to achieve live births. Conditions such as secondary infertility, uterine adhesions, and leiomyoma were more common among women who did not achieve live birth. IVF was the predominant ART procedure, with the majority of cycles utilizing the agonist stimulation protocol and favoring fresh embryo and cleavage stage transfers. The completeness of baseline data exceeded 99% (Supplemental table 3).

Association of blood pressure with assisted pregnancy outcomes

Of the 73,462 transfer cycles, 40,591 (55.3%) achieved live births. Compared with normotensive group (Supplemental table 4 and figure 1), LBR was significantly lower in the hypertensive group (48.1% versus 55.5%, adjusted RR (aRR) =0.919, 95%CI: 0.885-0.955, *P* <0.001), and the reduction of LBR in the anti-hypertensive treatment group had no statistical significance after adjusted for confounders (48.5% versus 55.5%, aRR=0.952, 95%CI: 0.863-1.049, *P* =0.320). RCS analyses did not reveal any non-linear associations between any blood pressure measure and LBR in either the normotensive or hypertensive datasets (*P* for non-linear >0.05, Figure 2, Supplemental figure 2 and 3). As showed in Table 1, Figure 2 and Supplemental figure 2, a 10mmHg increase in SBP was associated with a 1.2% (aRR per 10mmHg =0.988, 95%CI: 0.981-0.995, *P* =0.001) reduction in the likelihood of live birth in the normotensive group and a 5.4% (aRR per 10mmHg =0.946, 95%CI: 0.907-0.986, *P* =0.009) reduction in the hypertensive group. Meanwhile, DBP showed no significant association with LBR after adjustment.

Secondary outcome analyses in the normotensive subset (Table 1, Supplemental figure 4 and 5) revealed a significant association between SBP and a good birth outcome rate (aRR per 10mmHg =0.984, 95% CI: 0.973-0.995, *P*=0.005), but not with CPR. Increases in SBP (aRR per 10mmHg =1.052, 95% CI: 1.022-1.082, *P*<0.001) and DBP (aRR per 10mmHg =1.051, 95% CI: 1.013-1.091, *P*=0.009) were linked to higher risks of first trimester miscarriage in pregnancies that reached clinical stage. In the 39,041 cycles that achieved live birth, increases in SBP and DBP were significantly

associated with higher risks of GDM and gestational hypertension, with no significant associations found with duration of pregnancy, birth weight, or the Z-score of newborns in both singleton and twin live birth cycles. Moreover, no significant associations between SBP and small for gestational age were found in both singleton and twin live birth cycles (Supplemental table 5).

Sensitivity analyses

Sensitivity analyses, adhering to stricter ACC/AHA guidelines, showed consistent results with the main analysis regarding the association of SBP (aRR per 10mmHg =0.987, 95% CI: 0.977-0.997) or DBP (aRR per 10mmHg =0.998, 95% CI: 0.984-1.013) with LBR (Supplemental figure 6). Two additional strategies for screening confounding factors were applied to the initial normotensive dataset. Except for a negative association between an increase in DBP and birth weight (adjusted β per 10mmHg = -0.009, 95% CI: -0.017 - -0.001) in singleton live birth cycles, after adjusting for 16 confounding factors selected by LASSO regression, the trend relationships between SBP/DBP and other outcomes were consistent with the main analyses (Supplemental table 6).

Subgroup analyses

Subgroup analyses (Figure 3 and Supplemental table 7-18) indicated that the association between SBP and LBR lost significance in certain subgroups, including those beyond 30-40 years, with a BMI over 24 kg/m^2, and those with specific conditions or undergoing ART other than IVF. Meanwhile, the association between DBP and LBR

295 became statistically significant in subgroups of patients aged 30-35 years, with a BMI
296 less than 18.5 kg/m^2, and without male factor infertility or uterine adhesions. The varied
297 patterns of associations between blood pressure and both good live birth outcome and
298 first trimester miscarriage were similar to that of LBR across most subgroups. The
299 impact of pre-pregnancy blood pressure on the risk of developing gestational
300 hypertension was uniformly significant across all examined subgroups. Similarly, the
301 relationship between blood pressure and GDM held steady, except in subgroups over
302 35 years old, or those with a very low or high BMI, and those diagnosed with leiomyoma
303 or endometriosis. Moreover, Clinical pregnancy, ectopic pregnancy, 2nd or 3rd
304 trimester fetal loss, preterm birth and neonatal malformations remained independent
305 relationships with blood pressure across most subgroups.
306

307 **DISCUSSION**

308 For many decades, it has been well established by observational studies but also
309 placebo-controlled clinical trials that high blood pressure in adults, especially in the
310 second half of life, is causal for faster disease progression for diseases such as chronic
311 kidney disease, coronary heart disease and stroke that significantly shorten life
312 expectancy; see for example the statement of the WHO: Hypertension is a major cause
313 of premature death worldwide (https://www.who.int/news-room/fact-
314 sheets/detail/hypertension) (23–26). However, in our study, we were interested in the
315 impact of blood pressure on the key clinical outcome of IVF/ICSI treatment: LBR. Our

316 data indicated that during intrauterine life, maternal blood pressure also appeared to
317 be of particular importance. This study suggested that maternal SBP was associated
318 with the likelihood of having a healthy child in a very large cohort of women undergoing
319 IVF/ICSI treatment. This association was independent of known confounding factors
320 after IVF/ICSI treatment. The remarkable point was that this was not only true for the
321 relatively small group of women with preexisting hypertension, which was well known
322 from previous studies, but also for women with normal blood pressure according to the
323 current guidelines of the ISH for the diagnosis of hypertension. These criteria are the
324 valid criteria used during the data collection period for this study in China. But when
325 apply the somewhat stricter criteria of the ACH, basically nothing changed. Here, too,
326 it could be seen that blood pressure in the normal range was an essential outcome
327 parameter for the LBR after IVF/ICSI treatment.
328 Our data showed that SBP before the onset of pregnancy correlated better than DBP
329 with the end point of LBR. This was in good agreement with large blood pressure
330 studies in the general population, which also showed that SBP had a stronger impact
331 than DBP on cardiovascular events (27–29). To note in our study, however, was that
332 SBP measured immediately before the onset of pregnancy correlates inversely with
333 LBR after IVF/ICSI even in blood pressure ranges previously thought to be irrelevant
334 for clinical outcomes. Our data suggested a linear inverse relationship between SBP
335 and LBR. SBP refers to the maximum pressure within the large arteries when the heart
336 muscle contracts to propel blood through the body. Given that endothelial dysfunction

was particularly linked to SBP (30) and endothelial dysfunction was linked to pregnancy outcomes (31–33), subclinical endothelial dysfunction before initiation of IVF/ICSI treatment might contribute to adverse pregnancy outcomes linked in particular to SBP. In line with this hypothesis was the finding that gestational hypertension and GDM later in pregnancy were also associated with normal pre-pregnancy blood pressure levels according to current guidelines. This might indicate that these women (women aged 30-40 years old, with a low or normal BMI, and without clearly defined classical risk factors of infertility, see above) had a subclinical metabolic syndrome with endothelial dysfunction at the onset of pregnancy, which might have adversely affected the preterm birth rate and then ultimately the LBR. An association between metabolic syndrome and pregnancy outcome has been well-established in polycystic ovary syndrome (PCOS) (34–36). Our study might have two consequences: First, need for deeper mechanistic studies of common pathways of blood pressure regulation, endothelial dysfunction, and LBR. In addition, if our data can be confirmed in an additional huge observational study, a placebo-controlled treatment study to test the safety and efficacy of blood pressure lowering in infertile women with high normal blood pressure might be straightforward next step.

Unlike with a pregnancy without using ART, the course of pregnancy after artificial fertilization was tracked systematically in all study participants. Milestones such as CPR, ectopic pregnancy rate, and early and late miscarriage rate were well detectable. We therefore analysed these pregnancy milestones for their association with blood

pressure. The rate of clinical pregnancies, i.e., the first detection of vital fetus in the uterus by ultrasound, was not associated with blood pressure. In other words, very early stages of human pregnancy such as fertilization by IVF/ICSI, implantation of the embryo into the uterine mucosa, and very early development of the human embryo after IVF/ICSI treatment do not appear to be affected by maternal blood pressure in non-hypertensive women. The same was true for the rate of ectopic pregnancies. Clearly dependent on maternal DBP and especially SBP, however, was the first trimester miscarriage rate. In women conceiving without ART, maternal age is the leading cause of first trimester miscarriage probably due to chromosomal abnormalities. Besides maternal age, prior pregnancy loss, genital infections, diabetes, obesity, thyroid diseases, inherited thrombophilia, and substance abuse are also considered risk factors (37). Variations of SBP and DBP in the normal range according to current guidelines, however, were so far not considered as risk factors for early pregnancy loss in the general population as well as in women undergoing IVF/ICSI. However, our study clearly showed that differences in blood pressure range previously thought to be normal and insignificant for pregnancy outcome altered the risk of first trimester miscarriage. It remains to be demonstrated that this is also true for women conceiving without ART.

Hypertension-induced pregnancy loss is associated with major intrauterine growth retardation (38,39). Elevated blood pressure within the normal ranges might likewise contribute to our finding of a reduced LBR in women with high normal blood pressure

prior to pregnancy, since our data rather support first trimester miscarriage as key driver of our finding. We do, however, have no systematic ultrasound data on intrauterine fetal growth in our huge study population to finally prove this hypothesis.

The subgroup analyses enabled interesting insights, it told us in which group of women the blood pressure might be of greater importance for the success rate of the IVF/ICSI treatment. In other words, our data showed which clinical events in pregnancy after IVF/ICSI treatment were particularly sensitive to pre-pregnancy blood pressure.

Pre-pregnancy maternal blood pressure appeared to be particularly important for women aged 30-40 years or those with a BMI of 24 or lower (Figure 3). Women with endometrial thickness below the median of the study population also showed a significant dependence of LBR on blood pressure. In couples where male factors caused the couple's infertility, female blood pressure was less important. Pre-pregnancy blood pressure was also less important for the LBR of women with PCOS, uterine adhesions and leiomyomas. In summary, it can be concluded that blood pressure was more likely to play a more prominent role in older women, with lower BMI, and without clearly defined classical risk factor.

This study also has limitations. It was done at the largest IVF center in China and blood pressure data from over 70,000 women were analyzed. However, it is a single-center study. Center-specific effects cannot be excluded. The study participants were mainly Han Chinese. Thus, it must be shown whether the correlations found here can also be found in a Caucasian or African population, for example. The blood pressure

measurements were taken by an experienced nurse upon admission to the outpatient clinic. Blood pressure measurement by the nurses – and not the attending physician - can certainly reduce the white coat effect (40). The 24-hour blood pressure monitoring would certainly have been better, but this is not part of the clinical routine in IVF centers. Due to limitations in data availability, we did not collect some related factors and outcomes. It would also be interesting to know the family history of the study participants regarding hypertension. Knowledge about lifestyle factors that could be influenced and have an impact on blood pressure, such as salt consumption and physical activity, was also not recorded. For some subgroup analyses such as endometriosis, leiomyoma, and PCOS, group sizes were comparably small.

CONCLUSIONS

Notably, pre-IVF/ICSI SBP independently influenced treatment success, even in normotensive women. For decades, elevated blood pressure has been linked to diseases that reduce lifespan. Our study, if applicable also for women conceiving without ART – showed in addition the impact of blood pressure on LBR. These criteria for hypertension were established in the past decades using data focusing on cardiovascular diseases (41–43).

Correspondingly, our findings on blood pressure and LBR after infertility treatment align with general population data on cardiovascular outcomes. It is well established since decades that blood pressure within the normal range, especially in the high-

normal range, may adversely affect cardiovascular outcome (44,45). These findings have recently been confirmed in a very large observational study from Korea (46). It would be of huge interest to analyze, whether our results could be extended to women conceiving naturally, if so, it may suggest a need to reconsider blood pressure guidelines for women aiming to become pregnant. In addition to assessing cardiovascular risks, our data might suggest that guidelines for blood pressure in women of childbearing age should account for reproductive health, which holds significant clinical importance for this demographic.

Author Contributions

Berthold Hocher had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Berthold Hocher, Shujuan Ma

Acquisition, analysis, or interpretation of data: Shujuan Ma, Liang Hu, Huijun Chen, XiangWang Xu, Yvonne Liu, Johann-Georg Hocher, Fei Gong and Ge Lin.

Drafting of the manuscript: Shujuan Ma and Berthold Hocher.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Shujuan Ma, Liang Hu, Huijun Chen, XiangWang Xu.

Administrative, technical, or material support: Yvonne Liu, Johann-Georg Hocher, Fei Gong, Ge Lin.

Supervision: Berthold Hocher.

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Tables

Table 1. Pregnancy and prenatal outcomes of participants according to systolic and diastolic blood pressures as continuous variables in normotensive group.

	Number [a]	Frequency (%) / mean (SD)	Systolic blood pressure (per 10 mmHg)		Diastolic blood pressure (per 10 mmHg)	
			Adjusted RR/β (95% CI)	*P* value	Adjusted RR/β (95% CI)	*P* value
Transfer cycles						
Live birth	70,263	39,041 (55.6%)	0.988 (0.981 - 0.995)	0.001	0.992 (0.983 - 1.002)	0.104
Good birth outcome [b]	69,944	23,652 (33.8%)	0.984 (0.973 - 0.995)	0.005	0.991 (0.977 - 1.005)	0.217
Clinical pregnancy	70,263	45,755 (65.1%)	0.997 (0.991 - 1.003)	0.306	1.001 (0.994 - 1.008)	0.797
Ectopic pregnancy	70,263	844 (1.20%)	0.949 (0.883 - 1.019)	0.148	0.943 (0.859 - 1.034)	0.210
Clinical pregnancy cycles						
First trimester miscarriage	45,755	4820 (10.5%)	1.052 (1.022 - 1.082)	<0.001	1.051 (1.013 - 1.091)	0.009
2nd or 3rd trimester fetal loss	45,755	1833 (4.0%)	1.040 (0.992 - 1.091)	0.103	1.047 (0.984 - 1.114)	0.148
Live birth cycles						
Gestational diabetes	39,041	5906 (15.1%)	1.064 (1.038 - 1.090)	<0.001	1.106 (1.071 - 1.143)	<0.001
Gestational hypertension	39,041	1341 (3.4%)	1.587 (1.501 - 1.677)	<0.001	1.710 (1.587 - 1.843)	<0.001
Preterm birth	38,986	7546 (19.4%)	1.010 (0.988 - 1.032)	0.390	1.015 (0.987 - 1.043)	0.311
Neonatal malformation	39,041	659 (1.7%)	0.988 (0.911 - 1.071)	0.761	0.955 (0.860 - 1.061)	0.392
Singleton live birth cycles						
Duration of pregnancy, week	27,787	38.89 (1.62)	-0.014 (-0.035 - 0.006)	0.166	-0.018 (-0.044 - 0.009)	0.185
Birth weight, kg	27,660	3.27 (0.49)	-0.005 (-0.011 - 0.001)	0.119	-0.007 (-0.015 - 0.001)	0.091
Z-score [c]	27,554	0.20 (1.02)	-0.005 (-0.018 - 0.007)	0.417	-0.009 (-0.025 - 0.007)	0.270
Twin live birth cycles						
Duration of pregnancy, week	10,974	36.39 (2.01)	0.007 (-0.033 - 0.047)	0.734	0.002 (-0.050 - 0.053)	0.952

Birth weight, kg [d]	21,654	2.46 (0.46)	-0.001 (-0.009 - 0.007)	0.787	-0.003 (-0.014 - 0.008)	0.603
Z-score [cd]	21,461	0.10 (0.90)	-0.005 (-0.019 - 0.010)	0.523	-0.008 (-0.027 - 0.010)	0.383

Note: Multivariate Poisson regression was used for binary outcomes to estimate the risk ratios (RR), while multivariate linear regression was used for continuous outcomes, the adjusted factors included female age, infertility type, female body mass index, antral follicle count, anti-Müllerian hormone, untreated hydrosalpinx, leiomyoma, endometriosis, endometrial thickness, type of transfer, high-quality embryo transfer; Considering the interaction effect of systolic and diastolic blood pressures, we put them into the models separately.

[a], Sample size for inclusion in multivariate analyses after removal of missing covariates or outcome variables;

[b], Good birth outcome: defined as single live birth at greater than or equal to 37 weeks of gestation, with a birth weight between 2500 and 4000 g and without a major congenital anomaly;

[c], Z-score: defined as (infant birthweight - mean birthweight at the same gestational age for the same gender in the reference population) /standard deviation (SD) in the reference population);

[d], The association between birth weight / Z-score in multiple fetuses and female pre-pregnancy blood pressure was evaluated using a linear mixed effect model to consider cluster effects for multiple live births.

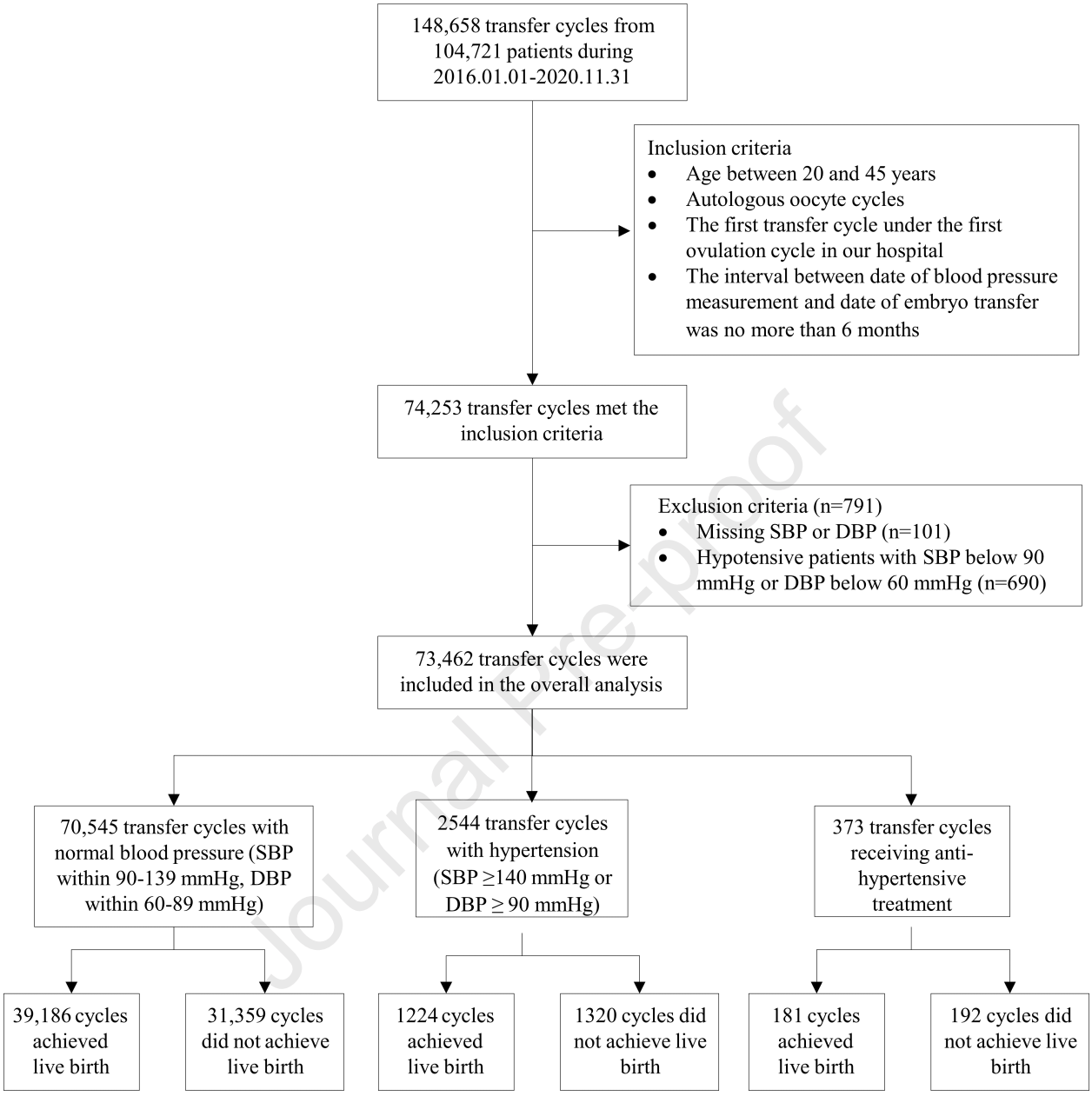
Figure legends

Fig 1. Study Flowchart. This figure presents the flow of participants through the study, detailing inclusion and exclusion criteria. DBP, diastolic blood pressure; SBP, systolic blood pressure.

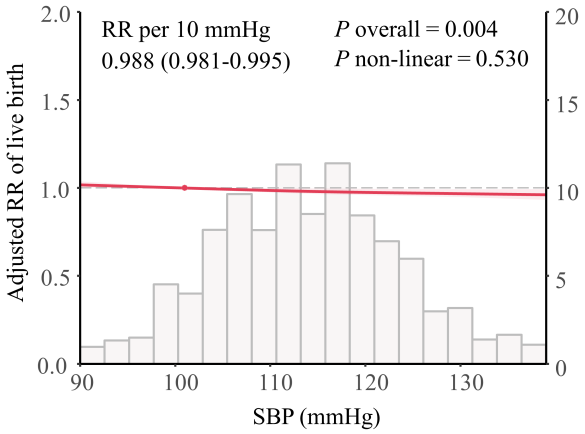
Fig 2. Adjusted Relationship Between Blood Pressure and Live Birth. The figure illustrates the adjusted RRs for live birth rate across normotensive (Panel A) and hypertensive (Panel B) groups, relative to blood pressure levels. The normotensive range was defined as SBP within 90-139 mmHg and DBP within 60-89 mmHg. Adjusted RRs (depicted as red lines) with their 95% confidence intervals (shown as pink shading) were based on restricted cubic spline models. These models assessed SBP and DBP on continuous scales, using the 10th percentile as reference points. Adjustment factors included demographics and clinical characteristics: female age, type of infertility, body mass index, antral follicle count, anti-Müllerian hormone levels, untreated hydrosalpinx, leiomyoma, endometriosis, endometrial thickness, transfer type, and high-quality embryo transfer. DBP, diastolic blood pressure; RR, risk ratio; SBP, systolic blood pressure.

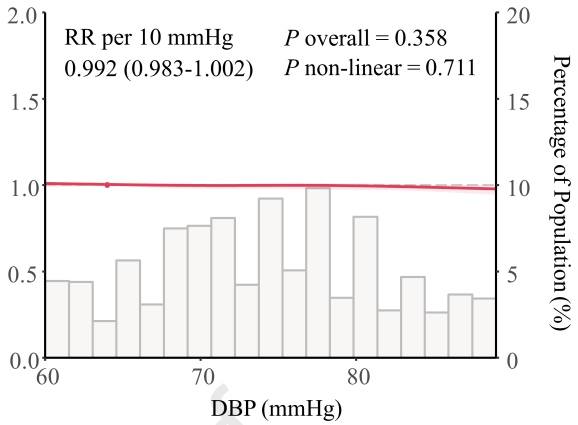
Fig 3. Subgroup Analysis Forest Plot for Blood Pressure and Live Birth Rate Association in Normotensive Subset. This forest plot displays the outcomes of multivariate Poisson regression analyses across various subgroups within the normotensive subset, exploring the relationship between blood pressure levels and live birth rates. The normotensive range was defined as SBP within 90-139 mmHg and DBP within 60-89 mmHg. Adjusted factors included female age, type of infertility, body mass index, antral follicle count, anti-Müllerian hormone levels, untreated hydrosalpinx, leiomyoma, endometriosis, endometrial thickness, transfer type, and high-quality embryo transfer. ART, assisted reproductive technology; BMI, body mass index; CI, confidence interval; ICSI, intracytoplasmic sperm injection; IVF, in

vitro fertilization; PCOS, polycystic ovary syndrome; PGT, preimplantation genetic testing; RR, risk ratio.

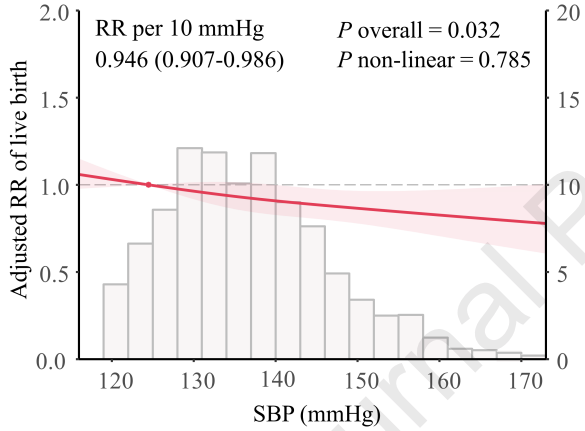


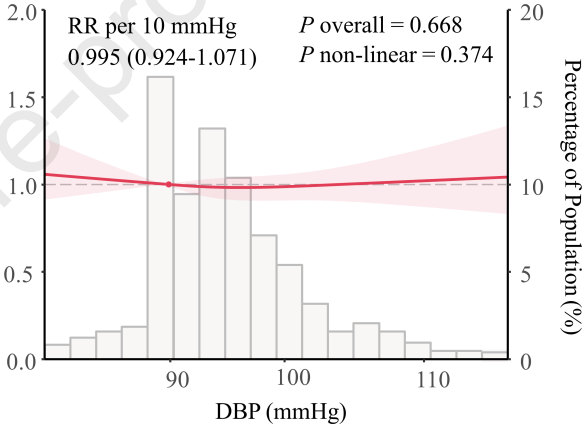
A: Normotensive subset





B: Hypertensive subset





Subgroup	Rate (events/patients)	Systolic blood pressure (per 10 mmHg) Adjusted RR (95% CI)	*P* value	Diastolic blood pressure (per 10 mmHg) Adjusted RR (95% CI)	*P* value
Overall	55.6% (39,041/70,263)	0.988 (0.981 − 0.995)	0.001	0.992 (0.983 − 1.002)	0.104
Female age					
20−30 years	63.1% (18,115/28,721)	1.001 (0.991 − 1.010)	0.918	0.999 (0.987 − 1.011)	0.864
30−35 years	57.6% (14,700/25,529)	0.985 (0.974 − 0.996)	0.010	0.983 (0.969 − 0.997)	0.020
35−40 years	44.6% (5397/12,113)	0.979 (0.960 − 1.000)	0.046	1.000 (0.973 − 1.028)	0.985
40−45 years	21.3% (829/3900)	1.020 (0.961 − 1.083)	0.511	1.058 (0.974 − 1.148)	0.180
Female BMI					
< 18.5 kg/m2	58.5% (3875/6620)	0.974 (0.952 − 0.996)	0.019	0.960 (0.933 − 0.988)	0.005
18.5−24 kg/m2	55.6% (28,520/51,289)	0.990 (0.982 − 0.998)	0.015	0.998 (0.987 − 1.009)	0.685
≥ 24 kg/m2	53.8% (6646/12,354)	0.991 (0.974 − 1.008)	0.298	0.990 (0.969 − 1.013)	0.399
Endometrium thickness					
≤ 12.4 mm	50.9% (18,175/35,708)	0.986 (0.975 − 0.997)	0.011	0.991 (0.978 − 1.005)	0.230
> 12.4 mm	60.4% (20,866/34,555)	0.992 (0.982 − 1.001)	0.067	0.994 (0.983 − 1.006)	0.331
Infertility tpye					
Primary	60.2% (17,609/29,266)	0.993 (0.983 − 1.003)	0.191	0.992 (0.979 − 1.005)	0.231
Secondary	52.3% (21,432/40,997)	0.985 (0.976 − 0.995)	0.003	0.993 (0.980 − 1.006)	0.273
Male factor					
No	54.4% (29,596/54,408)	0.986 (0.978 − 0.994)	0.001	0.988 (0.978 − 0.999)	0.032
Yes	59.6% (9445/15,855)	0.994 (0.981 − 1.008)	0.429	1.005 (0.987 − 1.023)	0.608
PCOS					
No	54.6% (32,392/59,351)	0.989 (0.982 − 0.997)	0.007	0.994 (0.984 − 1.004)	0.267
Yes	60.9% (6649/10,912)	0.985 (0.969 − 1.001)	0.069	0.988 (0.968 − 1.009)	0.248
Uterine adhesions					
No	56.7% (33,496/59,108)	0.986 (0.979 − 0.994)	<0.001	0.988 (0.979 − 0.998)	0.018
Yes	49.7% (5545/11,155)	1.001 (0.981 − 1.021)	0.936	1.020 (0.994 − 1.047)	0.132
Leiomyoma					
No	56.3% (35,393/62,865)	0.989 (0.982 − 0.997)	0.004	0.993 (0.984 − 1.003)	0.161
Yes	49.3% (3648/7398)	0.979 (0.956 − 1.002)	0.078	0.984 (0.953 − 1.015)	0.307
Endometriosis					
No	55.8% (35,488/63,549)	0.990 (0.982 − 0.997)	0.005	0.994 (0.985 − 1.003)	0.211
Yes	52.9% (3553/6714)	0.977 (0.954 − 1.000)	0.050	0.979 (0.949 − 1.010)	0.185
Gene/chromosomal abnormal					
No	55.2% (35,914/65,020)	0.989 (0.982 − 0.997)	0.004	0.992 (0.983 − 1.002)	0.116
Yes	59.6% (3127/5243)	0.975 (0.952 − 1.000)	0.049	0.992 (0.961 − 1.023)	0.609
Cycle type					
Fresh	57.1% (27,615/48,380)	0.990 (0.982 − 0.998)	0.015	0.993 (0.982 − 1.003)	0.173
Frozen	52.2% (11,426/21,883)	0.984 (0.970 − 0.997)	0.018	0.993 (0.975 − 1.010)	0.406
ART type					
IVF	55.4% (26,758/48,336)	0.990 (0.981 − 0.998)	0.018	0.992 (0.981 − 1.003)	0.132
ICSI	55.1% (7221/13,094)	0.985 (0.969 − 1.001)	0.064	0.990 (0.969 − 1.011)	0.331
IVF+ICS	56.7% (1932/3405)	0.993 (0.961 − 1.025)	0.656	1.004 (0.962 − 1.047)	0.860
PGT	57.6% (3123/5419)	0.981 (0.957 − 1.006)	0.131	1.003 (0.971 − 1.035)	0.867