# The effect of trigger day maximal follicle size greater than 25 mm on pregnancy result in patients receiving IVF-ET treatment.

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**Research Article**

**Keywords:** IVF-ET, trigger day, maximal follicle size, pregnancy outcomes

**Posted Date:** June 3rd, 2022

**DOI:** https://doi.org/10.21203/rs.3.rs-1643692/v1

## Abstract

# Background

Previous studies have involved the impact of the dominant follicle diameter on the number of eggs retrieved and pregnancy outcome during in vitro fertilization embryo transfer assisted pregnancy. In the natural physiological cycle of normal women, when the follicle diameter reaches 18–25 mm, it is discharged autonomously, while in the process of assisted reproduction, asynchronous follicular development often occurs, although these large follicles may not affect the level of reproductive endocrine. However, there is no study on whether giant follicles with a diameter of more than 25 mm on trigger day will affect pregnancy outcome.The goal of this study is to see whether a trigger day maximum dominant follicle diameter more than 25 mm affects the outcome of an IVF-ET pregnancy.

# Methods

From January 2018 to January 2021, 569 patients (610 cycles) underwent IVF-ET at a university Hospital's reproductive Center and were categorized based on whether the greatest dominant follicle diameter on trigger day was larger than 25 mm: Group A (n = 435, maximum dominant follicle diameter 25 mm), group B (n = 175, maximum dominant follicle diameter 25 mm). The cumulative live birth rate was the key outcome index, clinical pregnancy rate was the secondary outcome index, and additional outcomes were normal fertilization rate, embryo formation rate, and ectopic pregnancy rate.

# Results

The existence of follicles with a trigger day diameter greater than 25 mm may alter the result of IVF-ET, lowering the clinical pregnancy rate (40.92 percent vs 30.2 percent, P = 0.008) and the live birth rate (37.24 percent vs 27.43 percent, P = 0.017). Multivariate logistic regression study demonstrated that the presence of follicles with a diameter of more than 25 mm on trigger day was connected with the pregnancy result after embryo transfer. More prospective clinical trials are required to further investigate the influence of trigger day maximum follicle diameter on pregnancy outcome due to the limitations of this research and the paucity of prior studies on this issue.

# Conclusions

The maximal trigger day follicle diameter of more than 25 mm seems to impact the pregnancy outcome of IVF-ET, resulting in a somewhat unfavorable outcome, and the development of gigantic trigger day follicles should be avoided in clinical practice as much as feasible.

## Introducion

With the advancement of human assisted reproductive technology (ART), in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) have been acknowledged as successful treatments for infertility in recent years[1]. The success of IVF/ICSI is strongly reliant on age, endometrium, and embryological variables [2].

In the natural cycle, under normal circumstances, the follicle normally reaches 18-25mm in diameter and will spontaneously discharge. Human chorionic gonadotropin (HCG) is utilized to replicate luteinizing hormone (LH) peaks in order to stimulate ovulation as the follicle grows and finally matures in controlled superovulation. The timing of HCG injections is critical for getting high-quality eggs. In general, follicle diameter, estrogen level in peripheral blood, and the number of mature follicles all influence the time of HCG usage Meanwhile, the dosage and timing of HCG injections may be altered flexibly based on the patient's individual condition.

At the moment, the trigger is usually 2–3 follicles with diameters more than 17 mm or 18 mm [3, 4]. Previous research has shown that the maximal follicular diameter has an influence on pregnancy outcome. Despite discrepancies in results[3, 5], most studies still recommend HCG injection when the follicle diameter is ≥ 17 mm or ≥ 18 mm, and the fraction of mature follicles should be regulated within a particular range.

However, in clinical therapy, we discovered a phenomenon in which the highest follicle diameter on trigger day in certain patients surpassed 25 mm following routine and correct regulated hyper-ovulation while taking hormone levels and dominant follicle growth into consideration. Although this was unusual, it piqued our interest. Therefore, this research retrospectively assessed the influence of maximal trigger day follicle diameter above 25mm on IVF-ET result, in order to give valid evidence for timing selection and adjustment of hyper-ovulation technique.

## Materials And Methods

# Subject of Study

A retrospective cohort research was done on patients who had long-term IVF luteal phase long-term regimen at the reproductive center of a tertiary public hospital in Shandong Province from January 2018 to January 2021. The research included patients who satisfied the following criteria: Patients with an egg retrieval cycle age of 45 years old; Patients with a BMI of 18.50-24.99kg/m2; Patients whose infertility is caused by fallopian tube issues; Patients undergoing IVF fertilization; Patients undergoing luteal phase long-acting rectangular ovulation induction; Patients undergoing fresh embryo transfer following egg retrieval The following patients were barred from participating in the study: Patients who opted out of the cycle for different reasons; The man was diagnosed with severe oligoasthenospermia; Patients with preimplantation genetic testing (PGT) or preimplantation genetic diagnosis (PGD); Patients with endometriosis, polycystic ovary syndrome, luteinization of unruptured follicles, recurrent abortion and

immune and endocrine diseases that may affect fertility; Patients with either spouse's chromosomal abnormalities; Patients with genital deformities; Insufficient information.

Finally, 610 individuals were enrolled in the research. The included patients were separated into two groups based on whether the maximum follicular diameter on the trigger day exceeded 25mm: group A (n = 435, the maximum follicular diameter on the trigger day 25mm) and group B (n = 175, the maximum follicular diameter on the trigger day 25mm). The reproductive ethics committee of the Affiliated Hospital of Shandong University of Traditional Chinese Medicine (no.SDUTCM20211003) authorized the research. Informed consent from the patients was exempt because of the retrospective nature of the study.

# Review of Diagnosis and Treatment

After 5–7 days after ovulation in the menstrual cycle, and 0.8-1.875mg of gonadotropin-releasing hormone agonist (GnRH-a, Triptorelin, Ipsen Pharma biotech, France) was injected in the middle luteal phase, the sex hormone and B-ultrasound were detected 14 days later, and the down regulation standard was reached (the diameter of follicle was about 5mm; the thickness of endometrium was (Puregon, Merck, USA; or Gona-F, Merck, Germany; or u-FSH, Lizhu pharmaceutical, China). When ovulation induction reaches a particular degree, inject 5000–10000 U of hCG (Zhuhai Lizhu pharmaceutical, China), and collect eggs 35–37 hours later. The oocyte is fertilized by traditional insemination once the egg is taken up (standard IVF). Normal fertilization is defined as having two pronucleus-containing nuclei 16–18 hours after fertilization (2PN).

# Embryo transfer

Fresh embryo transfer: on the third- or fifth-day following egg retrieval, embryo transfer is performed using traditional procedures guided by ultrasonography. The number of embryos transplanted is decided by the patient's unique condition, which includes criteria such as age and embryo quality. High quality day 3 embryos were characterized as having at least six cells and 20% fragments; high quality day 5 blastocysts had a full blastocyst cavity, trophoblastic ectoderm, and inner cell quality score of AA, AB, BA, or BB [6]. In each cycle, at least one high-quality day 3 embryo, two poor day 3 embryos, or one high-quality day 5 embryo were transferred (none of the patients included in this study had blastocysts). Following transplantation, luteal support was administered. If pregnancy was confirmed, hormone medication was continued until the baby was 9–10 weeks old.

# Pregnancy Outcome Assessment

Fourteen days after donation - HCG level to indicate pregnancy; 5 weeks later, ultrasound scan revealed an intrauterine gestational sac and fetal heartbeat, indicating clinical pregnancy. An embryo obtained during an ovarian stimulation cycle and finally delivered live (gestation > 24 weeks) is considered a live birth. The primary observation indicator was the live birth rate, while the secondary observation index was the clinical pregnancy rate. Other observation indicators included IVF normal fertilization rate, embryo formation rate, high-quality embryo rate, abortion rate, ectopic pregnancy rate, etc.

# Statistical investigation

For data analysis, SPSS (version 21.0, Chicago, USA) software was utilized. For measurement data, the independent t-test or Mann Whitney U-test is employed for comparison based on the normality of distribution. Rates were used to convey the counting data. To assess the difference between independent samples, the Chi square test and the Fisher exact test were utilized. The link between the highest follicle diameter on the trigger day and the live birth rate was determined using binary logistic regression analysis. Simultaneously, possible covariates such as age, BMI, anti-Mullerian hormone (AMH), number of embryos transferred, and number of high-quality embryos transferred were included into the logistic regression model. $P<0.05$ was used to determine statistical significance.

## Results

# Patient starting point

This research involved 569 participants (610 IVF-ET cycles) who were separated into two groups. The maximal follicle diameter of 25 mm was not discovered on the trigger day of luteal long-acting rectangular ovulation induction in group A (n = 435), but it was found on the trigger day in group B (n = 175).There was no significant difference between the two groups at baseline,specific comparison data was presented in Table 1.

Table 1
Baseline characteristics of IVF-ETs

| characteristics | A group | B group | P-value |
|---|---|---|---|
| **Patients** | 411 | 158 | |
| **IVF-ET cycles** | 435 | 175 | |
| **Female age at oocyte retrieval** | 36.7 | 27.4 | 0.056 |
| **Duration of infertility** | 3.66 | 3.66 | 0.994 |
| **Body mass index** | 22.8 | 22.4 | 0.249 |
| **Anti-müllerian hormone** | 2.67 | 4.06 | 0.158 |
| **Basic FSH** | 8.02 | 7.32 | 0.090 |
| **Basic LH** | 4.79 | 4.39 | 0.221 |
| **Basic oestradiol** | 87.24 | 52.67 | 0.253 |

# Ovarian hyperstimulation cycle characteristics and outcomes

There was no significant difference between the two groups in ovarian stimulation days, total gonadotropin use, estradiol, luteinizing hormone and progesterone levels on the trigger day, total number of oocytes taken out, 2pn fertilization rate and the number of high-quality embryos formed(Table 2),. The

number of transplantable embryos generated by single egg retrieval was the only significant difference (4.18 vs 3.20, P<0.001).

Table 2
cycle features of IVF-ETs

| characteristics | A GROUP | B GROUP | P-value |
|---|---|---|---|
| **No of days of COS** | 11.43 | 11.20 | 0.231 |
| **Total Gn dose administered** | 2682.78 | 2570.59 | 0.117 |
| **Serum LH on trigger day** | 1.59 | 1.61 | 0.902 |
| **Serum estradiol on trigger day** | 3123.99 | 3255.05 | 0.317 |
| **Serum progesterone on trigger day** | 1.16 | 1.10 | 0.144 |
| **No of oocytes retrieved** | 11.36 | 11.23 | 0.758 |
| **2PN fertilization** | 7.43 | 6.91 | 0.150 |
| **No of embryos available for transfer** | 4.18 | 3.20 | <0.001* |
| **No of high-quality embryos** | 2.26 | 2.18 | 0.699 |

# Pregnancy and childbirth outcomes

There were significant differences in the clinical pregnancy rate (40.92 percent vs 30.29 percent, P = 0.008) and live birth rate (37.24 percent vs 27.43 percent, P = 0.017), but no significant differences in the abortion rate (2.07 percent vs 1.71 percent, P = 0.438) or ectopic pregnancy rate (1.61 percent vs 1.14 percent, P = 0.213). (Table 3). The greatest follicle diameter on the trigger day was more than 25 mm, which was inversely connected with clinical pregnancy rate and live birth rate, according to binary logistic regression analysis. Despite the fact that multivariate logistic analysis revealed no significant association after accounting for age, BMI, AMH, the number of implanted embryos, and the percentage of high-quality embryos (Table 4).

Table 3
pregnancy outcomes for both groups

| | A GROUP | B GROUP | P-value |
|---|---|---|---|
| **Clinical pregnancy** | 178(40.92%) | 53(30.29%) | 0.008* |
| **Clinical pregnancy loss** | 9(2.07%) | 3(1.71%) | 0.438 |
| **Ectopic pregnancy** | 7(1.61%) | 2(1.14%) | 0.213 |
| **Live birth** | 162(37.24%) | 48(27.43%) | 0.017* |

Table 4
analyscs for factors affecting clinical pregnancy,Live birth using binary logistic regression model

| | | Crude model | | Adjusted model | |
|---|---|---|---|---|---|
| | | OR (95% CI) | P-value | OR (95% CI) | P-value |
| Clinical pregnancy | A GROUP | Reference | | Reference | |
| | B GROUP | 0.614(0.423to0.890) | 0.01* | 0.394(0.067to2.899) | 0.441 |
| Live birth | A GROUP | Reference | | Reference | |
| | B GROUP | 0.637(0.433to0.936) | 0.022* | 0.403(0.064to2.545) | 0.334 |

# Discussion

We discovered that the maximal follicle diameter on the trigger day is too high, which might impair the outcome of assisted reproduction in vitro fertilization. Excess follicles may reduce the quality of follicles that can be removed during this cycle of ovarian hyperstimulation, resulting in the formation of a relatively small number of embryos that can be used for transfer and decreasing the possibility of clinical pregnancy and final live birth after embryo transfer. Although in the process of ovulation induction, excluding the patients' own ovulation dysfunction leading to the luteinization of unruptured follicles, it is unusual to have enormous follicles without early removal of follicles, it should nevertheless be avoided as far as feasible.

When hCG is utilized early, the appearance and function of follicles are not completely mature, and the LH receptor on follicular granulosa cells is not rich enough (7), so they cannot react adequately to hCG. According to Rubens fadini et al., hCG may stimulate the meiotic recovery of follicle oocytes with a diameter of 10-12mm and advance to the MII stage[8]. As a result, hCG can hardly affect the growth and development of small follicles, causing follicles to be excreted at the wrong time; or the cumulus complex is not loose enough and close enough to the follicular wall, the egg recovery rate is low, and even affects the maturity of oocytes, affecting the fertilization rate and pregnancy rate. Some research examined the major proteins influencing follicular maturation in follicular fluid from the standpoint of proteomics, and they examined the follicular fluid at various phases (9). It has been discovered that mature oocyte follicular fluid There are changes in the composition of immature oocyte follicular fluid and follicular fluid during ovulation, as shown by the combined action of mature oocytes, cumulus cells, and granulosa cells on the microenvironment (10, 11). The egg misses the optimal period for fertilization, the follicle expands to a certain amount, the oocyte is impacted by endogenous LH and prematurely restarts mitosis, resulting in a change in endometrial receptivity and missing the best time for fertilization and implantation.

Follicular formation must be well-regulated in order to provide highly developing oocytes for fertilization. Many components of ovarian follicular fluid (proteins, cell growth factors, peptide hormones, steroids, and so on) vary dynamically with oocyte growth and development and ultimately have a positive or negative effect in oocyte maturation (12).

The proper hCG injection time is critical for obtaining high-quality eggs (13, 14). There is no single standard for the maximum follicle diameter of the hCG trigger day at the moment. Mehri and colleagues Follicles bigger than 18 mm are thought to have mature oocytes with a high fertilization rate, but tiny follicles have a high aberrant or non-fertilization rate despite the fact that they may still contain mature oocytes (15); Wirleitner et al. Believe that follicles with a diameter of 13–23 mm have the best potential to generate high-quality blastocysts leading to live birth (16); studies have also indicated that in the antagonist regimen, more mature follicles may be obtained when the trigger day is chosen at a diameter of 12–19 mm (17). Nonetheless, it is difficult to uncover meaningful information in current research concerning the influence of maximum follicle diameter on oocyte retrieval result and pregnancy outcome when the greatest follicle diameter on the trigger day exceeds 25 mm. Follicles having a diameter more than 25mm had a detrimental influence on the result of in vitro fertilization in this investigation. Because the follicular fluid of such individuals was not examined for effective components as part of the retrospective study, it was unable to systematically detail the influence of large follicular fluid contents on pregnancy outcome from a micro viewpoint. We think that this is due to follicular over-maturing and alterations in associated proteins and growth hormones, which causes barriers to the maturation of additional oocytes (18). Furthermore, mature oocytes may contain larger quantities of estrogen. High estrogen levels shorten the implantation window and cause abnormal expression of implantation-related genes, including insufficient secretion of endometrium under high estrogen action, asynchronous development of glands and stroma, decreased expression of estrogen and progesterone receptors, and premature expression of pinocytes (19, 20).

On the trigger day, the highest follicle diameter in some individuals included in the trial surpassed 25mm. One cause might be that some patients are elderly. Female fertility declines with age, as does follicular cell activity, resulting in out-of-control follicular growth and development. Wu et al. discovered that granulosa cell proliferation reduces and apoptosis rises in aged women. Early egg retrieval in elderly individuals may (21). Second, some people who are not old have impaired ovarian function. Through clinical observation of non-elderly individuals with impaired ovarian reserve, Wu et al. Also showed that selecting the dominant follicle diameter line of 16 ~ 18 mm as the trigger time may acquire the greatest clinical pregnancy rate (22).

# Conclusion

In conclusion, our research reveals that in the long-term luteal phase ovulation induction therapy, the condition that the follicle diameter surpasses 25mm on the trigger day may signal a relatively poor pregnancy result, so that the trigger time should be considered. This research has several limitations, including a small sample size, a single site, and a retrospective design, and there have been few prior investigations on follicular fluid and endometrial receptivity. As a result, multicenter and large sample studies are still required to corroborate the findings in the follow-up, and further prospective clinical trials are required to further investigate the potential effect.

# Declarations

## Corresponding authors

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## Availability of data and materials

The datasets used or analysed during the current study available from the corresponding author on reasonable request.

## Ethics approval and consent to participate

The reproductive ethics committee of the Affiliated Hospital of Shandong University of Traditional Chinese Medicine (ref approval no.SDUTCM20211003) authorized the research and agreed to exempt the informed consents All procedures were carried out in accordance with relevant guide-lines and regulations and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

## Consent for publication

Not applicable.

## Acknowledgements

Not applicable.

## Author contributions

XX and SJY designed the study; XX and LJX responsible for data collection ,XFD and ZCC responsible for thesis writing; DL and SJY were in charge of data collection; and LF and SJY were in charge of data collection and supervision.

WHC attentively reviewed the article and took into consideration all elements of the work. The paper has been reviewed and approved by all authors. The paper has been reviewed and approved by all authors.

## Funding

This work was financed by the National Natural Science Foundation of China (82174429,81974577) and Shandong Provincial Natural Science Foundation project(ZR202102280473).

## Competing interests

The author has not signed any contract with any funding unit that might influence the study findings. All of the writers disclose that they do not have any conflicting interests.

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