Objective: We aimed to evaluate the future outcomes of patients undergoing their first IVF (in vitro fertilization) attempt with no oocyte retrieved, no normal zygotes formed, or no embryos available for transfer and to identify factors affecting the live birth rate.

Methods: Patients who underwent no transplantable embryo in their first IVF cycles but carried out several consecutive cycles between January 2012 to December 2020 were retrospectively enrolled and divided into three groups: group A (no egg retrieval), group B (no normal zygotes formed), and group C (no embryos available to transfer). The patients were also divided into the live birth group and non-live birth group according to whether they got a live baby or not. The clinical data and the cumulative clinical outcomes of groups were compared.

Results: 496 patients met the inclusion criteria and enrolled, with 121 patients with no oocytes retrieved in group A, 138 patients with no normal zygotes formed in group B, and 237 patients with no embryos available to transfer in group C. The age [(34.75(5.82) vs 31.91(5.31), P<0.001; 34.75(5.82) vs 32.25(5.72), P<0.001)] and baseline FSH level [(13.04(8.82) vs 10.52(7.39), P=0.005; 13.04(8.82) vs 9.91(5.95), P<0.001)] of women in group A were significantly higher than those in groups B and C. The stable cumulative live birth rate/patient of three groups achieved 18.18% (after 5 cycles, group A), 28.98% (after 3 cycles, group B) and 20.25% (after 7 cycles, group C). Moreover, the multivariate regression analysis showed that female age and ovarian reserve were main factors affecting the live birth outcome of patients with no embryo transfer in their first IVF cycle attempts.

Conclusions: The future clinical outcome may be better in women with no normal zygotes than those with no oocyte retrieved or no available embryo at their first IVF cycle attempts. The main factors influencing the live birth are age and ovarian reserve.

Keywords: in vitro fertilization, no embryo transfer, cycle cancellation rate, poor ovarian response, cumulative live birth rate
INTRODUCTION

Embryo transfer is a key step for successful pregnancy of women through assisted reproduction, but this process may face cycle cancellation because of no oocyte retrieved, no normal zygote formed, or no available embryos. Considering the inherent poor outcomes, most studies have excluded patients with cycle cancellation at the beginning of research (1–3). The ESPART study reported the prevalence of cycle cancellation was 4.7% in poor responders (4), and another survey showed the risk of cycle cancellation caused by poor ovarian response was about 20% (5). However, the prevalence in the general population receiving in vitro fertilization (IVF) is obscure. A French study examined medical factors associated with early cessation of IVF in 5135 couples and found that couples who did undergo no embryo transfer during the first IVF cycle attempt were more likely to stop treatment early (6). Other studies (7–10) have found that the psychological burden of failure in non-pregnancy treatment is the reason for withdrawing from further treatment. There are currently few reports on the clinical outcome of follow-up treatment in these patients, but it is necessary to provide these patients with information about the final clinical outcome in all institutions carrying out the artificial reproduction technology (ART).

Based on the above observational studies and to answer the consultation of patients with no transplantable embryo in their first IVF cycle attempt, this study was performed to investigate the outcome of future fertility of patients undergoing their first IVF cycle attempt with no embryos transplanted as well as to identify factors that might affect the possibility to get a baby in subsequent IVF cycle attempt.

MATERIALS AND METHODS

Subject

The retrospective study was performed in consecutive women attending the IVF procedure in our hospital from January 2012 to December 2020. Inclusion criteria were women who wanted more cycle attempts after their first IVF cycles had been cancelled for some reasons even if they had reached the oocyte pick-up (OPU) stage and had undergone egg retrieval in their first IVF cycle. The first delivery was used as the end point of the study. Exclusion criteria include: (i) chromosomal abnormalities in either their spouse or pre-implantation genetic testing cycles; (ii) patients who did not continue the IVF cycle after the first cancelled cycle; (iii) patients who had no clinical outcome at the end of follow-up. This study was approved by the ethics committee of our hospital, and all patients had signed the informed consent to participate (Figure 1).

Treatment Protocol and Pregnancy Criteria

The stimulation protocol was performed according to our center’s guidelines and was determined by the treating clinician based on individualized conditions. The stimulation protocol in fresh cycles included GnRH-a long protocol (luteal phase short-acting GnRH-a long protocol), short-acting GnRH-a protocol, GnRH-ant protocol (GnRH antagonist protocol), EFLL protocol (early-follicular phase long-acting GnRH agonist long protocol), PPOS protocol (progestin-primed ovarian stimulation protocol), and milder ovarian stimulation protocol. Different protocols may be used in the same person in different cycles.

Follicle growth and hormone levels were continuously monitored by ultrasound and blood tests. Human chorionic gonadotropin (hCG) was injected when the largest follicle diameter was bigger than 18 mm or the diameter of at least three follicles was bigger than 17 mm during the fresh cycle, and the oocytes were collected 36-38h after hCG injection. The oocytes were inseminated through conventional IVF/ICSI (intracytoplasmic sperm injection), and fertilization was observed 16-18h after insemination. Seventy-two hours after oocyte retrieval, whether to transplant or to freeze the embryo was based on embryo grading and the individual clinical situation of each patient. Blood β-hCG (+) was measured 14d after transfer as biochemical pregnancy, and clinical pregnancy was determined by ultrasonography at 28-30d when a gestational sac and primordial ventricular pulsation were observed.

Embryo Score and Cycle Outcome Definition

The ASEBIR scoring criteria was used to assess the embryo at the cleavage stage (11). Embryos were classified into grades I-IV according to the number of blastomeres on day 3, proportion of fragmentation, uniformity of blastomeres, multinucleation, number of vacuoles, and normalness of the zona pellucida. The criteria for good quality embryos were 2PN (2 pronucleus) origin, 7-9 cells, fragmentation <10%, and basic homogeneity of the cleavage. Non-transferable embryos were defined as embryos with grade IV with no fused embryos formed in further culture at Day3; non-insemination was defined as no MII (mature) eggs 2 hours after degranulation; non-fertilization was defined as no normal progenitor nuclei observed after IVF fertilization with no oocyte cleavage. Group B (no normal zygote formation group) included non-fertilization and no normal progenitor nuclei.

Grouping and Indicators

Patients were divided into three groups depending on the cause for the cancellation in their first IVF cycle: group A (no egg retrieval group), group B (no normal zygote formation group) including patients with non-insemination and non-fertilization, and group C (no embryos available to transfer). According to whether they had got a live baby or not, the patients were divided into live birth and non-live birth groups. The patients’ age, BMI (Body mass index), infertility years, infertility type, infertility factors (male or female), basic FSH or LH level, Gn (gonadotropin) dose and days, cumulative clinical pregnancy rate, and cumulative live birth rate of the three groups were compared. The Gn days, Gn dose, mean Oocytes/opu, total oocytes retrieved, average number of 2PN fertilization/opu, average number of transferred embryos/opu, cumulative clinical pregnancy rate/opu, cumulative clinical pregnancy rate/
patient, https://fanyi.baidu.com/translate?aldtype=16047&query=%E7%AC%AC%E4%B8%80%E5%91%A8%E6%9C%9F%E6%82%A3%E8%80%85%E7%89%B9%E5%BE%81&keyfrom=baidu&smartresult=dict&lang=auto2zh
##cumulative live birth rate/opu, https://fanyi.baidu.com/translate?aldtype=16047&query=%E7%AC%AC%E4%B8%80%E5%91%A8%E6%9C%9F%E6%82%A3%E8%80%85%E7%89%B9%E5%BE%81&keyfrom=baidu&smartresult=dict&lang=auto2zh

##cumulative live birth rate/patient were recorded, respectively, among three groups according to the cycle rank, and the basic characteristics including age, BMI, basic FSH or LH level, Gn dose and days between the live birth and non-live birth groups in the first cycle were investigated.

Statistical Analysis
The SPSS23.0 software (IBM, Chicago, IL, USA) was used for statistical analysis. Continuous variables were expressed as mean (standard deviation or SD) and categorical variable data were expressed as numbers and percentages. One-Way ANOVA was used to analyze the mean difference among groups, the Chi square test was used to compare the classified data between groups, and the binary Logistic regression (Enter) was used to calculate the OR (odds ratio) value. The statistically significant difference was set at $P<0.05$.

RESULTS
Subject
During the study period, a total of 19,657 couples underwent the first IVF cycle and with oocytes being picked up, and 837 patients had cycle cancellation in their first IVF cycle attempts. 298 women underwent only one IVF cycle, of which 50 women were with no egg retrieved, 48 women with no normal zygotes formed and 200 women with the cancellation cycle due to poor embryo quality. 496 women met the study inclusion criteria and were enrolled.

Cumulative Clinical Outcomes at Cycle Rank
In group A, the cumulative clinical pregnancy rates were 7.14% per OPU and 20.66% per patient, and the cumulative live birth rates were 6.28% per OPU and 18.18% per patient, all of which reached a plateau at the 5th OPU cycle (Table 2.1 and Figure 2).
### TABLE 1 | Comparison of baseline values and final reproductive outcomes in the first IVF cycle among the three groups.

| groups                                      | Group A | Group B | Group C |
|---------------------------------------------|---------|---------|---------|
| **Characteristics of patients in the first cycle** |         |         |         |
| Number of patients                          | 121     | 138     | 237     |
| Age (years)                                 | 34.75 (5.82) | 31.91 (5.31) | 32.25 (5.72) |
| BMI (kg/m2)                                 | 23.41 (3.71) | 23.70 (3.51) | 23.4 (3.51) |
| FSH/mIU                                     | 13.04 (8.82) | 10.52 (7.39) | <0.001 9.91 (5.95) |
| LH/mIU                                      | 5.81 (5.75) | 5.14 (4.03) | <0.001 7.93 (46.97) |
| AMH (ng/ml)                                 | 0.50 (0.56) | 0.68 (0.65) | <0.001 1.15 (1.53) |
| Infertility years                           | 4.42 (3.97) | 4.21 (3.33) | <0.001 4.29 (3.45) |
| **Infertility type**                        |         |         |         |
| Primary infertility                         | 61/121 (13.22%) | 91/138 (15.22%) | <0.001 132/237 (13.92%) |
| Secondary infertility                       | 60/121 (10.01%) | 47/138 (10.36%) | 0.011 105/237 (14.75%) |
| **Infertility factors**                     |         |         |         |
| Male (%)                                    | 16/121 (13.22%) | 21/138 (15.22%) | <0.001 33/237 (13.92%) |
| Tubal (%)                                   | 58/121 (47.93%) | 57/138 (41.30%) | <0.001 101/237 (42.62%) |
| Endometriosis (%)                           | 7/121 (5.79%) | 6/138 (4.35%) | <0.001 15/237 (6.33%) |
| Unexplained infertility (%)                 | 5/121 (4.13%) | 13/138 (9.42%) | <0.001 20/237 (8.44%) |
| Uterine factor (%)                          | 2/121 (1.65%) | 3/138 (2.17%) | <0.001 0/237 (0.00%) |
| Ovulatory disorder (%)                      | 25/121 (20.66%) | 28/138 (20.29%) | <0.001 46/237 (19.41%) |
| Others (%)                                  | 4/121 (3.31%) | 46/138 (33.33%) | <0.001 4/237 (1.69%) |
| **Ovarian stimulation protocol**            |         |         |         |
| GnRH-a long protocol                        | 15/121 (<0.001) | 46/138 (70/237) | <0.001 70/237 (<0.001) |
| EFLL protocol                               | 7/121 (0.011) | 17/138 (41/237) | <0.001 41/237 (0.005) |
| GnRH-ant protocol                           | 30/121 (0.004) | 22/138 (72/237) | <0.001 72/237 (ns) |
| Others                                      | 69/121 (0.004) | 54/138 (54/237) | <0.001 54/237 (0.001) |
| Gn days (days)                              | 7.67 (4.98) | 9.28 (3.30) | <0.001 9.93 (3.68) |
| Gn dose (IU)                                | 2126.01 (1474.67) | 2367.66 (1127.77) | <0.001 2622.98 (1138.61) | 0.063

**Clinical outcome**

|                           |         |         |         |
|---------------------------|---------|---------|---------|
| Number of OPU cycles      | 350     | 366     | 610     |
| Clinical pregnancy (n)    | 25      | 54      | 60      |
| Live birth(n)             | 22      | 40      | 48      |
| Cumulative clinical pregnancy/opu (%) | 25/350 (7.14%) | 54/366 (14.75%) | <0.001 60/610 (9.84%) |
| Cumulative clinical pregnancy/patient (%) | 25/121 (20.66%) | 54/138 (39.13%) | 0.005 60/237 (25.32%) |
| Cumulative live birth/opu (%) | 22/350 (6.28%) | 40/366 (10.92%) | <0.001 48/610 (7.88%) |
| Cumulative live birth/patient (%) | 22/121 (18.18%) | 40/138 (28.98%) | <0.001 48/237 (20.25%) | 0.054

Values are presented as number or mean (SD).

EFLL protocol, early-follicular phase long-acting GnRH agonist long protocol.

Others of ovarian stimulation protocol mean PPOS protocol, short-acting GnRH-a protocol, micro stimulation protocol, etc. ns, non-singificant.
The cumulative live birth rates/patient in group B was 28.98% and did not increase any more after cycle 3 (Table 2.2 and Figure 2), whereas the cumulative live birth rates/patient in group C was 20.25% and reached a plateau after cycle 7 (Table 2.3 and Figure 2).

**Comparison Between Live Birth and Non-Live Birth Groups and Factors Influencing Live Birth**

Both age (31.21 ± 4.65 vs 33.22 ± 5.95, P=0.001) and basic FSH level (9.08 ± 6.15 vs 11.41 ± 7.49, P=0.004) in the live birth group were statistically significantly lower than those in other groups (Table 3). The multivariate regression analysis showed that age and basic FSH level were predict factors for live birth (ORadjusted 0.935, 95% CI 0.876-0.997, P=0.042; ORadjusted 0.937, 95% CI 0.878-0.999, P=0.046) (Table 4).

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**Table 2.1** | IVF cycles’ characteristics and their final reproductive outcomes of group A stratified according to IVF cycle rank.

| cycle rank | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|------------|---|---|---|---|---|---|---|---|---|----|
| Gn days    | 7.57 | 7.99 | 9.04 | 7.26 | 7.36 | 7.67 | 5.00 | 2.00 | 5.50 | – |
| (4.90)     | (3.68) | (4.86) | (4.02) | (3.64) | (3.56) | (2.65) | (2.12) |     |     |    |
| Gn dose    | 2100 | 2148 | 2545 | 1892 | 1932 | 1800 | 1225 | 300 | 1425 | – |
| (1476)     | (1184) | (1798) | (1345) | (1356) | (1168) | (943) | (954) |     |     |    |
| No. of patients of opu with zero oocytes/total patients of opu | 121/16 | 121/16 | 121/16 | 121/16 | 121/16 | 121/16 | 121/16 | 121/16 | 121/16 | 121/16 |
| Mean Oocytes/opu | 0.27 | 0.77 | 1.80 | 1.96 | 1.77 | 1.00 | 1.33 | 1.00 | 2.00 | – |
| Number Fertilizes oocytes of 2PN | 0 | 166 | 166 | 166 | 166 | 166 | 166 | 166 | 166 | 166 |
| Average number of 2PN fertilization/opu | 0 | 2.07 | 1.67 | 1.56 | 1.33 | 0.67 | 1.00 | 1.00 | 1.00 | – |
| Number of high quality embryos | 0 | 43 | 17 | 7 | 2 | 1 | 0 | 0 | 0 | – |
| Average number of high quality embryos/opu | 0 | 0.57 | 0.55 | 0.44 | 0.29 | 0.33 | – | – | – | – |
| Number of transferred embryos | 0 | 53 | 25 | 8 | 5 | 2 | 1 | 1 | 1 | 1 |
| Average number of transferred embryos/opu | 0 | 1.77 | 1.39 | 1.60 | 1.67 | 1.00 | 1 | 1 | 1 | 1 |
| total patients of opu | 121 | 121 | 121 | 121 | 121 | 121 | 121 | 121 | 121 | 121 |

Values are presented as number or mean (SD).

**DISCUSSION**

This study evaluated the chance of a live birth in women with no embryo transfer at their first IVF cycle attempt over their subsequent IVF treatment course and factors affecting the live birth.

In our center, the total cycle cancellation rate was nearly 10%, and the cancellation rate of the first cycle was 4.9%. This may be related to embryo transfer strategies as well as the ovarian stimulation protocols used in our hospital. For example, the cycle cancellation rate of low ovarian response with minimal stimulation was 10% while that with long ovarian stimulation protocols used in our hospital. For Siristatidis et al (14) also found that the
TABLE 2.2 | IVF cycles’ characteristics and their final reproductive outcomes of group B stratified according to IVF cycle rank.

| cycle rank | 1    | 2    | 3    | 4    | 5    | 6    | 7    | 8    | 9    | 10   |
|------------|------|------|------|------|------|------|------|------|------|------|
| Gn days    | 9.28 | 8.32 | 8.91 | 6.72 | 8.14 | 7.0(1.63) | 8    | 2    | 8    | 12   |
| (3.30)     | (3.65)| (3.56)| (3.01)| (2.08)|      |      |      |      |      |      |
| Gn dose    | 2367 | 2242 | 2369 | 1633 | 2121 | 1650 | 2400 | 300  | 1800 | 3600 |
| (1127)     | (1154)| (1194)| (797)| (716)|      | (851)|      |      |      |      |
| Total of oocytes retrieved | 571  | 560  | 162  | 55   | 22   | 6    | 4    | 2    | 2    | 3    |
| Mean Oocytes/opu | 4.17 | 4.59 | 3.51 | 2.89 | 2.44 | 1.50 | 2    | 1    | 2    | 3    |
| (5.70)     | (4.81)| (3.57)| (3.70)| (2.92)| (1.00)|      |      |      |      |      |
| Number Fertilizes oocytes of 2PN | 0    | 173  | 56   | 15   | 14   | 2    | 2    | 2    | 2    | 3    |
| Average number of 2PN fertilization/opu | 0    | 3.20 | 1.93 | 1.36 | 2.00 | 0.67 | 2    | 2    | 2    | 3    |
| (0.37)     | (2.99)|(1.12) | (2.71)| (0.577)|      |      |      |      |      |      |
| Number of high quality embryos | 0    | 57   | 15   | 6    | 3    | 0    | 0    | 0    | 0    | 3    |
| Average number of high quality embryos/opu | 0    | 0.78 | 0.60 | 0.67 | 0.60 | –    | –    | –    | –    | –    |
| (1.85)     | (1.96)| (1.66)| (0.89)|      |      |      |      |      |      |      |
| Number of transferred embryos | 0    | 93   | 19   | 3    | 0    | 2    | 0    | 0    | 0    | 0    |
| Average number of transferred embryos/opu | 0    | 1.82 | 1.73 | 1.50 | –    | –    | 2    | 2    | –    | –    |
| (0.66)     | (0.66)| (1.15)|      |      |      |      |      |      |      |      |
| Number of no normal zygotes/opu | 138  | 7    | 3    | 0    | 1    | 1    | 0    | 0    | 0    | 0    |
| total patients of opu | 138  | 138  | 50   | 22   | 10   | 4    | 1    | 1    | 1    | 1    |
| 138  | 0    | 42   | 9    | 1    | 2    | 0    | 0    | 0    | 0    | 0    |

Values are presented as number or mean (SD).

In the group with no egg retrieved, the proportion of the patients in the first IVF cycle cancellation was 21.54% [(121 + 50)/(496 + 298)], and 22 of these women achieved a live birth in their subsequent cycles. Furthermore, there was no significant difference in the cycle source and the mode of fertilization through analysis of the original data. In patients with no eggs being retrieved in our study, the ovarian response was low, and their average age was higher than those in the other two groups. In the end, a 18% cumulative live birth rate was achieved in these patients after the 5th IVF cycle, which was similar to that of the

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TABLE 2.3 | IVF cycles’ characteristics and their final reproductive outcomes of group c stratified according to IVF cycle rank.

cycle rank | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10
--- | --- | --- | --- | --- | --- | --- | --- | --- | --- | ---
Gn days | 9.97 | 9.366 | 8.25 | 8.69 | 8.06 | 9.43 | 5.00 | 6.66 | 7.00 | 7.50
(3.63) | (2.92) | (3.80) | (4.07) | (3.51) | (4.54) | (4.24) | (5.13) | (9.90) | (0.71)
Gn dose | 2621 | 2427 | 2150 | 2181 | 2107 | 1882 | 1087 | 1300 | 1575 | 1887
(1136) | (883) | (1153) | (1368) | (1280) | (917) | (1007) | (1128) | (2227) | (159)
Total of oocytes retrieved | 1079 | 1367 | 288 | 66 | 47 | 17 | 3 | 4 | 3 | 4
Mean Oocytes/opu | 4.55 | 5.84 | 4.57 | 2.34 | 2.94 | 1.89 | 0.60 | 1.33 | 1 | 2
Number Fertilizes oocytes of 2PN | 374 | 467 | 144 | 29 | 17 | 8 | 2 | 2 | 2 | 1
Average number of 2PN fertilization/opu | 1.82 | 3.16 | 3.35 | 1.53 | 1.42 | 1.14 | – | – | – | –
(2.65) | (3.50) | (5.61) | (1.17) | (1.08) | (0.37) | – | – | – | –
Number of high quality embryos | 0 | 42 | 6 | 3 | 1 | 1 | 0 | 0 | 0 | 0
Average number of high quality embryos/opu | 0 | 0.45 | 0.26 | 0.33 | 0.14 | 0.20 | 0 | – | – | –
(1.06) | (0.54) | (0.50) | (0.38) | (0.447) | – | – | – | – | –
Number of transferred embryos | 0 | 18 | 189 | 2 | 2 | 2 | – | – | – | –
Average number of transferred embryos/transplantation cycle | 0 | 1.68 | 1.89 | 2 | 2 | 2 | – | – | – | –
(0.63) | (0.61) | – | – | – | – | – | – | – | –
No transplantable embryo/opu | 237 | 237 | 67 | 30 | 16 | 10 | 5 | 3 | 3 | 2
No transplantable embryo | 0 | 41 | 6 | 7 | 4 | 1 | 1 | 0 | 0 | 0

total patients of opu
https://fanyi.baidu.com/translate?aldtype=16047&query=%E7%AC%AC%E4%B8%80%E5%91%A8%E5%8C%9F%E6%82%A3%E8%80%85%E7%89%B9%E5%BE%81&keyfrom=baidu&smartresult=dict&lang=auto2zh - zh/en/javascript:void(0);Number of clinical pregnancies
https://fanyi.baidu.com/translate?aldtype=16047&query=%E7%AC%AC%E4%B8%80%E5%91%A8%E5%8C%9F%E6%82%A3%E8%80%85%E7%89%B9%E5%BE%81&keyfrom=baidu&smartresult=dict&lang=auto2zh - zh/en/javascript:void(0);Number of clinical pregnancies
https://fanyi.baidu.com/translate?aldtype=16047&query=%E7%AC%AC%E4%B8%80%E5%91%A8%E5%8C%9F%E6%82%A3%E8%80%85%E7%89%B9%E5%BE%81&keyfrom=baidu&smartresult=dict&lang=auto2zh - zh/en/javascript:void(0);Number of clinical pregnancies
values are presented as number or mean (SD).

study by Raoul Orvieto et al. (16). For these patients, the reproductive outcome will not change after the 5th IVF OPU cycle being tried, and the next ovulation stimulation cycle is suggested to be abandoned. Nonetheless, the patient’s own decision should always be respected.

The proportion of women with no normal zygotes formed in the first IVF cycle cancellation was 23.43% [(138 + 48)/(496 + 298)], and 40 of the 138 patients achieved a live birth eventually. In our hospital, when the number of eggs retrieved was less than or equal to 3, ICSI was not rescued. The majority of these patients had fewer eggs retrieved, which might be one reason for fertilization failure. Even though there was no significant difference in the fertilization methods (IVF vs ICSI) in the live birth cycle (9.46% vs 13.27%), 54 cases were changed to ICSI after the first cycle of IVF, and 13 cases obtained a live birth, with the live birth rate of 24.07%. According to these outcomes, changing the mode of insemination in the second cycle may bring a better outcome. Some scholars (17) found that compared with the hCG single trigger group, the oocyte fertilization rate (73.1% vs 58.6%), clinical pregnancy rate (33% vs 20.7%), live birth rate
(26.9% vs 14.5%), abortion rate (17.4% vs 37.0%), and embryo transfer elimination rate (6.1% vs 15.4%) in the double trigger group were significantly different. This may suggest that changing the trigger scheme, grasping the correct trigger time so as to get the target follicles as far as possible, and getting the MII (mature) eggs may improve the pregnancy outcomes. Furthermore, some patients may improve the clinical outcomes by using some new techniques like AOA (assisted oocyte activation), IVM (in vitro maturation), and testing for associated genes. A retrospective study (18) showed that AOA intervention after ICSI fertilization failure significantly increased the normal fertilization rate (52.1%), the cumulative clinical pregnancy rate (47.1%) and the live birth rate (29.4%).

The proportion of patients with the cancellation cycle caused by poor embryo quality in the first IVF cycle was 55.04% [(237 + 200)/(496 + 298)]. These patients are more challenging for the

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**TABLE 3** | Basic characteristics of the first cycle in live birth group and non-live birth group.

|                          | Live birth group | non live birth group | p   |
|--------------------------|------------------|----------------------|-----|
| Proportion of patients   | 0.06             |                      |     |
| Group A                  | 22               | 99                   |     |
| Group B                  | 40               | 98                   |     |
| Group C                  | 48               | 189                  |     |
| Age (years)              | 31.21 (4.65)     | 33.22 (5.96)         | 0.001|
| BMI (kg/m2)              | 22.36 (3.55)     | 23.51 (4.14)         | ns  |
| FSH/mIU                  | 9.08 (6.15)      | 11.41 (7.49)         | 0.004|
| LH/mIU                   | 5.43 (4.05)      | 7.02 (3.72)          | ns  |
| Infertility years        | 4.05 (3.24)      | 4.37 (3.62)          | ns  |
| AMH (ng/ml)              | 1.71 (2.91)      | 1.06 (1.18)          | ns  |
| Infertility type         | ns               |                      |     |
| Primary infertility      | 65               | 219                  |     |
| Secondary infertility    | 45               | 167                  |     |
| Ovarian stimulation protocol |              |                      |     |
| GnRH-a long protocol     | 35               | 96                   |     |
| EFLL protocol            | 20               | 45                   |     |
| GnRH-ant protocol        | 21               | 103                  |     |
| others                   | 34               | 142                  |     |
| Gn days (days)           | 10.05 (3.98)     | 8.99 (3.95)          | 0.01|
| Gn dose (IU)             | 2464 (1121)      | 2428 (1265)          | ns  |

Values are presented as number or mean (SD).

EFLL protocol, early-follicular phase long-acting GnRH agonist long protocol.

Others of ovarian stimulation protocol mean PPPOS protocol, short-acting GnRH-a protocol, micro stimulation protocol, etc.

ns, non-significant.
ART. In our study, these patients’ age was not high, they had more eggs, but the CLBR was low. In the ovulation induction of these patients, 25 cases with the antagonist regimen obtained a live birth, whereas 23 cases with other protocols did not. It seems that the antagonist regimen had a trend of increasing the live birth rate, but no significant difference was found in our study (10.25% vs 6.28%, P =0.07). Similarly, the fertilization mode of the live birth cycle was not significantly different. Moreover, although no differences were found in various infertility factors among these patients in our study, a recent study (19) reported that AOA could improve the clinical pregnancy and live birth rate in patients with male factors (oligoasthenospermia [OAT]), advanced age, polycystic ovary syndrome (PCOS), and unexplained infertility. In current literature, blastocyst transfer after ICSI-AOA according to different infertility factors may help to improve the clinical outcome of these patients. Besides, shortening the embryo culture time to the first or second day and carrying out gamete transfer or zygote transfer may be a goodway to improve the reproductive outcome of patients with embryonic development block from the embryologists’ point of view.

Female age and ovarian reserve are still the main factors influencing the live birth of patients with first IVF cycle cancellation. However, clinical quality control, personalized treatment, or changes in ovulation induction and fertilization mode may help them achieve a live birth. Therefore, for patients with good financial resources, the findings of the present study suggest extending the number of OPU cycles up to the 3rd, 5th, or 7th cycle even if the reasons for cancellation of the first IVF cycle are different.

Some limitations existed in this study, including the retrospective and one-center design, a small cohort of patients, and Chinese patients enrolled only. Moreover, the reasons for patient cycle cancellation are multifarious and complex, and patients with non-fertilization, fertilization failure and abnormal fertilization might have been assigned to one group for analysis, which limits the ability to control for potential unknown confounding factors. All these factors may affect the

| TABLE 4 | Multivariate regression analysis of IVF cycle between the live birth group and non-live birth group. |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                | Live birth group | non live birth group | P      | OR value (95% CI) | P      | OR adjusted value (95% CI) |
| ----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Number of cycles | 110             | 1216            |                |                 |                 |                 |
| Cycle outcome type | Not transplanted | 0               | 785            | –    |  –              | –    |  –              | –    |  –              |
| Fresh cycle transplantation | 65              | 227             | –              | –    |  –              | –    |  –              | –    |  –              |
| https://fanyi.baidu.com/translate?aldtype=16047&query=%E7%AC%AC%E4%B8%80%E5%91%A8%E6%9C%9F%E6%82%A3%E8%80%85%E7%99%89%E5%BE%81&keyfrom=baidu&smartresult=dict&lang=auto2zh - ##Thawed embryo transfer from Whole embryo freezing |
| Fertilization mode | No insemination | 0               | 217            | –    |  –              | –    |  –              | –    |  –              |
|                   | IVF             | 65              | 664            | –    |  –              | –    |  –              | –    |  –              |
|                   | ICSI            | 45              | 335            | –    |  –              | –    |  –              | –    |  –              |
| Patient first cycle type | Type A | 22              | 328            | 1    | 1              | 1    | 1              |
|                   | Type B          | 40              | 326            | 0.388 | 1.28          | 0.189 | 0.438          |
|                   |                 |                 |                | (0.726, 2.28) | (0.189, 0.500) |   |                 |
|                   | Type C          | 48              | 562            | 0.272 | 1.33          | 0.091 | 3.174          |
|                   |                 |                 |                | (0.802, 2.11) | (0.091, 0.998) |   | (0.884, 3.345) |
| age              | 31.21           | 33.22           | 0.04           | 0.956 | 0.042        | 0.935  | 0.876, 0.997   |
| (4.65)           | (5.95)         |                 |                | (0.916, 0.998)  | (0.042, 0.935) |   |                 |
| BMI              | 23.36           | 23.51           | ns             | 0.984 | ns           | 1.030  | ns             |
| (3.55)           | (4.14)         |                 |                | (0.928, 1.043)  | (0.985, 1.100) |   |                 |
| FSH              | 9.08            | 11.41           | 0.032          | 0.953 | 0.046        | 0.937  | 0.878, 0.999   |
| (6.15)           | (7.49)         |                 |                | (0.911, 0.996)  | (0.046, 0.937) |   |                 |
| LH               | 5.43            | 7.02            | ns             | 0.999 | ns           | 1.000  | ns             |
| (4.05)           | (3.722)        |                 |                | (0.994, 1.005)  | (0.996, 1.004) |   |                 |
| Gn days          | 10.05           | 8.99            | ns             | 1.067 | ns           | 1.073  | (0.984, 1.171) |
| (3.98)           | (3.95)         |                 |                | (0.964, 1.181)  | (0.973, 1.173) |   |                 |
| Gn dose          | 2464            | 2428            | ns             | 1     | ns           | 1      | ns             |
| (1122)           | (1265)         |                 |                |       |             |       |                 |

Values are presented as number or mean (SD), the OR (odds ratio) value and 95% CI (confidence interval), and OR adjusted value (95% CI) are obtained by adjusting the male factor, ovarian stimulation program and other confounding factors. ns, non-significant.
generalization of the outcome of this study. Future studies will have to resolve all these issues for better outcomes.

In conclusion, future clinical outcomes may be better in women with no normal zygotes than those with no oocyte retrieved or no available embryo at their first IVF cycle attempts. The main factors influencing the live birth are age and ovarian reserve.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of The Second Hospital of Hebei Medical University. The patients/participants provided their written informed consent to participate in this study.

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AUTHOR CONTRIBUTIONS

Study design: ZZ and GH. Data collection: XZ, MC, ZY, and PL. Data analysis: XZ and MC. Supervision: YX. Writing the original article: MC. Revision: ZZ. All authors contributed to the article and approved the submitted version.

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