The time interval between hCG priming and oocyte retrieval in ART program: a meta-analysis

Wei Wang · Xue-Hong Zhang · Wei-Hua Wang ·
Ya-Li Liu · Li-Hui Zhao · Shi-Long Xue · Ke-Hu Yang

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Abstract

Objective To evaluate the relationship between different hCG priming-to-oocyte retrieval intervals and assisted reproductive technology (ART) outcome.

Methods We systematically searched PubMed, EMBASE, the Cochrane Library, Science Citation Index, Chinese biomedicine (CBM) literature database, and Chinese Journal Full-text Database for randomized controlled trials (RCTs) published up to November 2010. Data was extracted from the studies by two independent reviewers. Statistical analysis was performed with Cochrane Collaboration's Review Manager (RevMan) 5.0.2. From extracted data, Risk Ratio (RR) with 95% confidence interval (CI) was calculated.

Results 5 RCTs totaling 895 participants were included. Oocyte maturation rate was higher in the long interval group compared with short interval group (RR, 0.67; 95% CI, 0.62–0.73). There were no significant difference between the two

groups with regard to fertilization rate (RR, 0.99; 95% CI, 0.94–1.04), implantation rate (RR, 0.91; 95% CI, 0.40–2.04), and pregnancy rate (RR, 0.79; 95% CI, 0.58–1.08).

Conclusion The percentage of mature (MII) oocytes can be increased by prolonging the interval between hCG priming and oocyte retrieval. The prolonged interval could not increase the fertilization rate, implantation rate, and pregnancy rate. Although there was evidence to confirm the results, they still need to be confirmed by large-sample, multicenter, randomized controlled trials. The time interval dependent mechanisms responsible for ART performance need to be elucidated.

Keywords Human chorionic gonadotropin · Oocyte retrieval · Time interval · Infertility · Assisted reproductive technology · Meta-analysis

Abbreviations

ART	Assisted reproductive technology
ATP	Adenosine triphosphate
CC	Clomiphene citrate
COH	Controlled ovarian hyperstimulation
ET	Embryo transfer
FSH	Follicle-stimulating hormone
GnRH-a	Gonadotropic hormone releasing hormone analogue
hCG	Human chorionic gonadotropin
hMG	Human menopausal gonadotropin
ICSI	Intracytoplasmic sperm injection
IGF	Insulin-like growth factor
IL	Interleukin
IM	Intramuscular injection
IUI	Intrauterine insemination
IVF	In vitro fertilization
IVM	In vitro maturation
LH	Luteinizing hormone

Capsule In ART treatment cycles, the chances to achieve a pregnancy are critically dependent on the retrieval of a suitable number of high quality oocytes and embryos. Angiotensin II, vascular endothelial growth factor (VEGF), interleukin I (IL-1), IL-6, IL-8, angiopoietin, insulin-like growth factor (IGF), basic fibroblast growth factor (bFGF), and endothelin levels appear able to identify women candidate for an ART treatment from whom a suitable number of high quality oocytes may be retrieved.

W. Wang · X.-H. Zhang (✉) · W.-H. Wang (✉) · L.-H. Zhao · S.-L. Xue

The Reproductive Medicine Center,
the First Hospital of Lanzhou University,
Lanzhou, China
e-mail: zhang.xuehong@yahoo.com.cn
e-mail: wangweihua11@yahoo.com

Y.-L. Liu · K.-H. Yang
The Evidence-Based Medicine Center of Lanzhou University,
Lanzhou, China

LI	Long interval
MII	Metaphase II
NA	Not available
RCT	Randomized controlled trial
RevMan	Review Manager
RR	Risk ratio
SI	Short interval
TUS	Transvaginal ultrasound
VEGF	Vascular endothelial growth factor
2PN	Two-pronuclear
95% CI	95% confidence interval

Introduction

During controlled ovarian hyperstimulation (COH), the natural endogenous Luteinizing Hormone (LH) surge often does not appear, or has appeared with improper timing and magnitude. Therefore, exogenous gonadotropin is needed to replace the endogenous LH surge. The most commonly used exogenous LH is human chorionic gonadotropin (hCG), which simulates the physiologic effects of LH, and is used to trigger the final follicular maturation before oocyte retrieval in ART program [1]. The interval between hCG priming and oocyte retrieval is very important, because a series of crucial processes, such as the start of luteinization, expansion of cumulus cells, and the resumption of oocyte meiosis are accomplished in the interval [2]. Many factors, such as the final products of renin angiotensin system, angiotensin II, vascular endothelial growth factor (VEGF), interleukin I (IL-1), IL-6, IL-8, angiopoietin, insulin-like growth factor (IGF), basic fibroblast growth factor, and endothelin are also involved in follicular development, oocyte maturation, fertilization, and embryo development. All of these substances have an effect in a time-dependent manner after hCG priming [3–5]. For example, VEGF can increase follicular vascularization and thus optimize dissolved oxygen content in follicle and consequently increase follicular maturation and oocyte quality. The follicular fluid VEGF level was significantly higher in the hCG +38 h oocyte retrieval group compared with the hCG +34 h oocyte retrieval group (2276.0 ± 790.1 versus 1946.6 ± 954.5 pg/ml, $P < 0.001$) [5]. On the day of hCG administration, serum IL-6 concentration was 8.40 ± 6.68 pg/ml, and 7.10 ± 0.68 pg/ml on the day of oocyte retrieval [6]. So the optimal time interval between hCG priming and oocyte retrieval has been encountered controversy, whether prolonged interval (>36 h) has any influence on the ART outcome, such as oocyte maturation rate, fertilization rate, implantation rate, and pregnancy rate.

Physiologic studies suggest that ovulation occurs anytime from 24 to 56 h after the onset of LH surge, with a

mean time of 32 h [7]. Nader et al. [8] studied the pharmacokinetics of hCG and its relation to ovulation and concluded that ovulation may occur earlier than 36 h in some women, they advised aiming for a <35 h interval if ovulation is to be avoided. In most in vitro fertilization (IVF) programs, the commonly practiced interval was 32 to 36 h that was derived from the studies on patients who used Clomiphene Citrate (CC) and/or human menopausal gonadotropin (hMG) for ovulation induction [9–11]. However, several studies [2, 12–14] had shown that ideal ART performance can be obtained when oocyte retrieval was done more than 36 h (up to 39 h) after hCG priming. Successful fertilization in vitro of oocytes retrieved 60 h after hCG injection was reported in 1998 [15]. The prolonged luteinization-to-oocyte retrieval increased the production of oocytes with fully expanded cumulus, which may reflect oocyte maturation, then researchers presumed that the subsequent proportion of oocytes proceeding to fertilization and cleavage also increased, implying that a longer interval may improve gamete quality by allowing more optimal in vivo maturation. Significantly more high quality cleaving embryos had been reported to be obtained when the interval was 38 h rather than 36 h [12]. Meanwhile, there were studies [16, 17] indicated that there was no significant difference on the outcome of IVF treatment cycles among the interval prolonged. Therefore, we carry out a meta-analysis to determine whether a prolonged hCG-to-oocyte retrieval interval is beneficial to ART outcome.

Methods

Inclusion criteria

We included randomized and quasi-randomized controlled trials that provided original analyses on the relationship between different hCG priming-to-oocyte retrieval intervals and ART outcome. Infertility patients presented with indications, such as primary infertility, tubal factor, male factor, or unexplained indication, underwent their ART treatment cycles and reported the outcome. We included participants from the general population were in good general health, besides infertility, without other diseases. The COH protocols were performed by combined therapy of gonadotropic hormone releasing hormone analogue (GnRH-a) and hMG or follicle-stimulating hormone (FSH).

We excluded studies in which the hCG was added to the culture medium rather than injection for patients. Studies in which the outcome data were not clearly defined were excluded. Reviews letters, commentaries, case reports, and editorials were also excluded if they did not contain original data. If multiple published reports from the same study

were available, only the one with the most detailed information for original data and outcome was included.

Literature search

We systematically searched PubMed, EMBASE, Cochrane Library, Science Citation Index, Chinese biomedicine (CBM) literature database, and Chinese Journal Full-text Database (from their inception to November 2010) for randomized controlled trials (RCTs), using the text and key words in combination both as MeSH (Medical Subject Headings) terms and text words. The search strategy used the following main search terms: “human chorionic gonadotropin” in combination with “interval”. We hand-searched reference lists of every retrieved study and reviewed relevant studies for additional publications. We searched the National Institute of Health, National Research Register, Current Controlled Trials, and Trials Central for unpublished studies and those in progress. We also used search engine such as Google™ to search for related references on the Internet. The search was restricted to human studies and without language restriction. Two reviewers (Wei Wang and Ya-Li Liu) independently assessed the titles and abstracts of all identified studies to confirm fulfillment of inclusion criteria; disagreements were resolved in consultation with a third reviewer (Ke-Hu Yang).

Types of intervention

Types of intervention were short time interval (<36 h) between hCG priming and oocyte retrieval versus long time interval (>36 h) between hCG priming and oocyte retrieval in the ART treatment cycles.

Types of outcome measures

The outcome measures of ART program were: oocyte maturation rate, defined as percentage of mature (MII) oocytes, metaphase II oocytes were defined by the presence of first polar body and round ooplasm. Fertilization rate, defined as the mean number of two-pronuclear (2PN) zygotes divided by MII-aspirated oocytes. Implantation rate, defined as percentage of transferred embryos of all embryos available for transfer. Pregnancy rate was calculated by considering clinical pregnancy, determined by the visualization of a viable gestational sac within the uterine cavity by ultrasound 3–4 weeks after embryo transfer.

Quality assessment

The methodological quality of included studies was assessed independently by two reviewers (Wei Wang and

Ya-Li Liu) according to the criteria stated in The Cochrane Collaboration Handbook [18]. For each study, the risk of bias assessed and tabulated for each of the following items: sequence generation, allocation concealment, blinding (participants, personnel, outcome assessors, and data analysts), incomplete outcome data, selective outcome reporting, and other sources of bias. Judgement of ‘Yes’ indicates low risk of bias, ‘No’ indicates high risk of bias, and ‘Unclear’ indicates unclear or unknown risk of bias. Disagreements were resolved by discussion with a third reviewer (Ke-Hu Yang).

Data extraction

Two reviewers, Wei Wang and Ya-Li Liu extracted data independently from full text papers. Differences were resolved by discussion with a third reviewer (Ke-Hu Yang). For each study, we extracted the following information: first author, year of publication, location of study, sample size, patients’ characteristics, such as mean age, duration of infertility, causes of infertility, usage and dose of hCG, and different methods of ART.

Statistical analysis

Data was analyzed by using the Cochrane Review Manager (RevMan) 5.0.2 to mix the extracted data for summary effect estimates and generate forest plots. Results for dichotomous variables would be expressed as Risk Ratio (RR) with 95% confidence interval (CI). We used fixed-effect model for calculations of summary estimates and their 95% CIs unless there was significant heterogeneity, in which result was confirmed by using the random-effect model. For the summary of each total or subtotal, we provided the χ^2 -test statistic for heterogeneity across studies with its degree of freedom and *P* value, the statistic I^2 that measured the extent of inconsistency in results, and the *Z* statistic with *P* value for overall effect. Generally, values of I^2 above 50% are deemed to suggest large heterogeneity, values of 25–50% are deemed to show modest heterogeneity, and values below 25% are deemed to represent low heterogeneity. However, these estimates can have large uncertainty, especially in the presence of few trials, and should be interpreted with caution [19].

Results

Literature search results

Detailed search procedures were summarized in the flow diagram (Fig. 1) illustrating the mechanisms of exclusion for certain studies in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-

Fig. 1 Flow diagram of search strategy

Analyses: The PRISMA Statement [20]. The search strategy retrieved 326 potentially eligible studies and subsequently excluded 321 studies with the following reasons: 308 were not relevant to the contents we interested; two were cohort studies and 1 used case-control design; five were with different experiment designs [21–25], the time interval referred to hCG-to-intrauterine insemination (IUI) or hMG-to-hCG rather than hCG-to-oocyte retrieval; three were missing test group or control group [12, 26, 27]; one was missing available outcome data [10]; one was duplicate publication [17]. Finally, 5 RCTs [13, 16, 17, 28, 29] totaling 895 participants were included in this meta-analysis.

The methodological quality of included studies

One trial [28] described odd or even IVF identity numbers of patients were used for the allocation of patients, this trial was known as quasi-randomized trial. Of the five included studies, only 1 trial [13] mentioned blinding: the gynecologist who performed the oocyte aspiration was blinded to the time interval, and only 1 trial [17] had adequate allocation concealment described: randomization was performed by drawing of sealed envelopes by a nurse who was not an active participant in the study. There was no losing of follow-up, the outcome data was complete, and without selective reporting bias. The

Table 1 Methodological quality assessment of included studies

Study	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting bias	Other bias
Raziel A (2006) [28]	IVF identity number	Unclear	Unclear	Yes	Yes	Unclear
Nargund G (2001) [16]	Unclear	Unclear	Unclear	Yes	Yes	Unclear
Björcke S (2000) [17]	Unclear	Yes	Unclear	Yes	Yes	Unclear
Mansour RT (1994) [13]	Unclear	Unclear	Yes	Yes	Yes	Unclear
Jamieson ME (1991) [29]	Unclear	Unclear	Unclear	Yes	Yes	Unclear

IVF in vitro fertilization

Table 2 COH protocols of ART treatment cycles

Study	Controlled Ovarian Hyperstimulation (COH)
Raziel A (2006) [28]	Triptorelin or Nafarelin + hMG or recombinant preparations
Nargund G (2001) [16]	GnRH-a Buserelin acetate + hMG
Bjercke S (2000) [17]	GnRH-a Suprefact + FSH
Mansour RT (1994) [13]	GnRH-a Buserelin acetate + hMG
Jamieson ME (1991) [29]	GnRH-a Buserelin acetate + hMG

methodological quality of included studies was summarized in Table 1.

The characteristics of included studies

The retrieved five trials were done in Israel, England, Norway, Egypt, and Scotland respectively from 1991 to 2006. One trial described the ethical approval that was obtained from the local research ethics committee [16]. Three trials applied IVF treatment cycles and two trials applied intracytoplasmic sperm injection (ICSI) treatment cycles. Two trials reported the ART outcome oocyte maturation rate, four trials reported the fertilization rate, two trials reported the implantation rate, and four trials reported the pregnancy rate. The COH protocols of the five studies were performed by combined therapy of GnRH-a and hMG or FSH (Table 2). The characteristics of included studies were summarized in Table 3.

Meta-analysis results

The meta-analysis results of outcome measures were shown in Table 4.

Oocyte maturation rate, defined as percentage of mature (MII) oocytes, MII oocytes were defined by the presence of

first polar body and round ooplasm. Figure 2 showed the Risk Ratio with 95% CI of oocyte maturation rate associated with interval between hCG priming and oocyte retrieval in randomized studies, a total of 1624 oocytes were retrieved in two eligible studies [13, 28], there were 1,020 oocytes reached MII. The oocyte maturation rate was significantly higher when oocyte retrieval >36 h after hCG injection compared with oocyte retrieval <36 h after hCG injection (RR, 0.67; 95% CI, 0.62–0.73; $I^2=33\%$).

Fertilization rate, defined as the mean number of 2PN zygotes divided by MII-aspirated oocytes. Figure 3 showed the Risk Ratio with 95% CI of fertilization rate associated with interval between hCG priming and oocyte retrieval in randomized studies, a total of 3455 MII oocytes were retrieved in four eligible studies [13, 17, 28, 29], there were 2285 MII oocytes fertilized into 2PN zygotes. The fertilization rate did not differ significantly between short interval group and long interval group (RR, 0.99; 95% CI, 0.94–1.04; $I^2=47\%$).

Implantation rate, defined as percentage of transferred embryos of all embryos available for transfer. Figure 4 showed the Risk Ratio with 95% CI of implantation rate associated with interval between hCG priming and oocyte retrieval in randomized studies, a total of 488 embryos available for transfer in two eligible studies [17, 28], there were 62 embryos transferred on the ET (embryo transfer) day. Since the implantation rate was heterogeneous ($I^2=58\%$) among the included studies, random-effect model was used to confirm the result (Fig. 5). There was no statistically significant difference between short interval group and long interval group (RR, 0.91; 95% CI, 0.40–2.04; $I^2=58\%$).

There were no differences in the pooled results of the two studies between fixed effect model and random effect model, although the weighted proportion for each study was changed. So the tendency of implantation rate was not changed.

Pregnancy rate was calculated by considering only clinical pregnancy, determined by the visualization of a

Table 3 Characteristics of included studies

Study	Location of study	Sample size (SI/LI)	Mean age (years)	Mean duration of infertility (years)	Causes of infertility	Usage and dose of hCG	ART
Raziel A (2006) [28]	Israel	72 (36/36)	31.3±4.9	5±3.6	Primary infertility	5000 IU, IM	ICSI
Nargund G (2001) [16]	England	533 (258/275)	33.4	NA	Tubal damage, male factor, and unexplained infertility	10000 IU, NA	IVF
Bjercke S (2000) [17]	Norway	170 (83/87)	SI: 35 LI: 33	NA	Tubal factor	10000 IU, subcutaneously	IVF
Mansour RT (1994) [13]	Egypt	60 (30/30)	SI: 32.6±3.1, LI: 31.2±2.3	NA	Male factor	10000 IU, IM	ICSI
Jamieson ME (1991) [29]	Scotland	60 (30/30)	NA	NA	Tubal factor or unexplained infertility	5000 IU, NA	IVF

SI short interval (<36 h); LI long interval (>36 h); IM intramuscular injection; IVF in vitro fertilization; ICSI intracytoplasmic sperm injection; NA not available

Table 4 Meta-analysis results of ART outcome measures

Outcome measures	No. of trials	Heterogeneity (I^2 , %)	Statistical model	Effect size	95% CI	<i>P</i> value
Oocyte maturation rate	2	33	Fixed	RR	0.67(0.62–0.73)	<0.00001
Fertilization rate	4	47	Fixed	RR	0.99(0.94–1.04)	0.64
Implantation rate	2	58	Random	RR	0.91(0.40–2.04)	0.81
Pregnancy rate	4	18	Fixed	RR	0.79(0.58–1.08)	0.13

viable gestational sac within the uterine cavity by ultrasound 3–4 weeks after embryo transfer. Figure 6 showed the Risk Ratio with 95% CI of pregnancy rate associated with interval between hCG priming and oocyte retrieval in randomized studies, a total of 835 patients were included in four eligible studies [16, 17, 28, 29], and 137 patients become pregnant after embryo transfer. The pregnancy rate did not differ significantly between the two groups (RR, 0.79; 95% CI, 0.58–1.08; $I^2=18\%$).

Discussion

The number of included studies is relatively small. The small number of participants and included studies, as well as the low quality of most studies, might not allow for a reliable conclusion. Adequate randomization can prevent selection bias in allocating interventions to participants. However, proper randomization is not always possible in the clinical context of infertility, as patients' choices have to be taken into account such as work and travel arrangements. Future study should describe how to generate the randomized allocation sequence. For example, opaque, sealed envelopes mentioned herein were used to conceal allocation. Blinding participants to the time interval might reduce the impact of subjective psychological factors. Blinding the doctors who perform oocyte retrieval, outcome assessors, and data analysts to the time interval could ensure that the compared groups receive similar attention, treatment and assessment. Without effective blinding might result in performance bias and measurement bias. In this meta-analysis, the follow-up time just was the interval

between hCG priming and oocyte retrieval. Most infertility patients were willing to cooperate with doctors with better compliance, there was no losing of follow-up unless suffered spontaneous ovulation to cancel the treatment cycle, thus the outcome data was relatively complete. Further research should pay attention to the impact of geographic differences. We still need more high-quality, multicenter, randomized controlled trials from other countries and regions.

There were two kinds of hCG dose used in the five studies, two studies used 5000 IU and three studies used 10000 IU. The hCG dose was determined according to the patients' responding to COH, levels of estradiol. An hCG dose of 5000 IU can give similar results compared to a dose of 10000 IU in terms of oocyte maturation rate, fertilization rate, and pregnancy rate, regardless of the route of administration. So the differences between hCG dose does not affect the ART outcome [30, 31]. The causes of infertility showed in the five studies were primary infertility, tubal factor, male factor, or unexplained infertility. These causes above are the very indications for IVF or ICSI, and their differences dose not interfere with the outcome of ART. Only one study described the duration of infertility, further study should describe the information of patients in detail with similar demographics to compare the baseline conditions roundly.

The timing of oocyte maturation in vivo after an injection of hCG was first estimated by Jagiello [32]. Of the five retrieved studies, the comparison was based on the short interval versus long interval: 35.3±0.7 versus 38.6±1.2 h, 33 versus 41 h, 34 versus 38 h, 35 versus 37 h, and 34 versus 39 h. The short interval varied from 33 to 36 h,

Fig. 2 Oocyte maturation rate of short interval versus long interval in ART program

Fig. 3 Fertilization rate of short interval versus long interval in ART program

while the long interval varied from 36 to 41 h. Van Steirteghem et al. reported that of the oocytes retrieved 33–36 h after hCG priming, 85% were in the MII stage [33]. Steptoe and Edwards reported that the preovulatory oocytes were in the predicted stage about 35 to 36 h after hCG injection [34]. In stimulated cycles with CC or hMG, ovulation can occur between 32 h and 36 h [35]. Mansour et al. [13] concluded that oocyte maturity was attained 36 h after hCG injection, and therefore oocyte recovery should not be performed before 36 h. Fertilization rate and cleavage rate were significantly higher in oocytes retrieved >36 h after luteinizing stimulus than in those <36 h after luteinizing stimulus. So we defined the 36 h as the demarcation to determine short interval group and long interval group.

Natural ovulation after LH surge may occur between 30 h and 36 h, whereas ovulation after hCG injection may occur between 36 h and 40 h in superovulation cycles without the use of GnRH-a [10]. Nevertheless, in the five included studies, the COH protocols were performed by combined therapy of GnRH-a and hMG or FSH. The use of COH protocols is intended to produce large cohorts of follicles and oocytes by creating continuous pituitary suppression and eliminate endogenous gonadotropin fluctuations. It is well known that with GnRH-a COH there is an implicit LH suppression and a longer in vivo maturation time than is possible without the use of GnRH-a. By producing a hypogonadotropic condition it

is possible to control the follicular development more readily and reduce the variations in response to hCG.

The hCG was administered when a sufficient number of follicles had developed, typically more than three follicles ≥ 17 mm in mean diameter, and the transvaginal ultrasound (TUS) guided approach was used for oocyte retrieval.

One of our concerns was the possibility of spontaneous ovulation before the scheduled time for oocyte retrieval as a result of prolonged exposure to hCG. Andersen et al. [36] found a mean time interval of 38.3 h from hCG injection to first follicular rupture. Nargund et al. concluded that no women ovulated up to 41 h from hCG administration. Fleming et al. reported that no ovulation occurs within a delay of less than 39.5 h [14]. Gudmundsson et al. [2] described 39 h as the critical time to avoid spontaneous ovulation. Of the five included studies, a patient from 38 h group [17] encountered spontaneous ovulation. We should control the interval properly to avoid cancelling the treatment cycles as a result of spontaneous ovulation.

Since the hours after luteinizing stimulus is a period of intense nuclear and cytoplasmic activity in human oocytes, so the interval between hCG priming and oocyte retrieval probably determines the degree of cellular and cytogenetic maturation. A prolonged interval would have an increased intrafollicular influence, yield oocytes in which all processes are completed, allow more in vivo maturation, and therefore more likely to develop into 2PN zygotes and high quality

Fig. 4 Implantation rate of short interval versus long interval in ART program (Fixed-effect model)

Fig. 5 Implantation rate of short interval versus long interval in ART program (Random-effect model)

normal cleaving embryos. The incidence of fully expanded cumulus cells is increased in the patients with longer interval (>36 h), and this apparent benefit is reflected in higher fertilization rate and cleavage rate. Immature oocytes are firmly attached to the follicular wall and not easy to aspirate; when oocytes reach maturity, this attachment becomes loose and oocytes are easily retrieved [37]. The procedure becomes easier and faster, flushing of oocytes with its potential disadvantages is avoided. In addition, extension of the in vivo maturation might reduce the incidence of polyspermy.

Oocyte meiotic maturation is an important factor for achieving fertilization and developing high quality embryos. Delaying oocyte retrieval to a longer interval is helpful to improve oocyte maturity, while there is no significant improvement in fertilization rate, implantation rate, and pregnancy rate. Son WY et al. obtained the similar results in their programmed in vitro maturation (IVM) cycles [38]. Apart from the time required for hCG to become available after administration analyzed herein, ART outcome is also associated with other factors as follows. The age of patient: the oocytes quality would become poorer with increased age of women. The number of mitochondria in the cytoplasm is reduced, incidence of DNA mutation is increased, adenosine triphosphate (ATP) is reduced, active oxygen is increased, and aneuploidy is increased, thus the developmental potential of oocytes and embryos are decreased [39]. The number of transferred embryos: although more embryos transfer could increase pregnancy rate, multiple pregnancy is also

increased [40]. When implanted ≥ 3 embryos, the pregnancy rate has not increased any more, the risk of multiple pregnancy is increased. In women under 35 years of age, transferring double high-quality embryos can help maximize clinical pregnancy rate while minimizing multiple pregnancy rate. Moreover, elective single embryo transfer with an acceptable pregnancy rate might be considered if a top quality embryo is available. The pregnancy rate of once-transfer was 40%, and the cumulative pregnancy rate was 60%, equal to even higher than the cumulative pregnancy rate of double-embryo transfer [41–43]. The quality of embryos (cleavage speed and morphologic distribution): embryos that absence of multinucleated blastomeres, four or five blastomeres on day 2, seven or more cells on day 3, and $\leq 20\%$ anucleated fragments are considered as top quality embryos [44]. The majority of embryos selected for transfer were at the 4-cell stage on day 2 at 42 h post-insemination. It is clear that 4-cell embryos on day 2 are more likely to be good grade embryos on day 3 and that 3-cell and greater than 4-cell embryos have poor developmental potential. Considering cell number at a set time (42–44 h post-hCG), even (two and four cells) rather than uneven (3, 5 and greater) cell numbers were significant in positive pregnancy events. The transition from 2-cell to 4-cell requires that the embryo proceeds through a 3-cell phase first and then rapidly cleaves again to form a 4-cell tetrahedron embryo [45–47]. If an embryo is cleaving too fast, relevant to all other embryos, it is most likely abnormal

Fig. 6 Pregnancy rate of short interval versus long interval in ART program

or has a cytokinetic abnormality [48, 49]. Endocrine profile: during COH, E_2 increased too much is not good for embryo nidation and increased LH might produce granulosa cells that prematurely luteinize, affecting the quality of embryos and pregnancy outcome. Immunity factors: presence of various antibodies, such as anti-sperm antibody, anti-endometrial antibody, anti-ovarian antibody, anti-cardiolipin antibody, anti-human chorionic gonadotropin antibody and so on, binding with corresponding antigens could result in antigen-antibody reactions, activate complement system, induce autoimmunity reaction, finally influence the pregnancy events. So we must take these factors into consideration sufficiently when carrying out ARTs.

Oocyte retrieval after hCG priming can be done at any time within a relatively broad interval. This flexibility of hCG-to-oocyte retrieval provides more convenience both for patients and physicians. The meta-analysis results also suggest that the temporal relationship between LH surge, follicle rupture, oocyte retrieval, and the potential for successful pregnancy during natural and artificial assisted menstrual cycles is needed to be learned.

Conclusion

The results indicate that the percentage of mature oocytes can be increased by prolonging the interval between hCG priming and oocyte retrieval. The fertilization rate, implantation rate, and pregnancy rate do not differ significantly between oocyte retrieval <36 h after hCG injection and oocyte retrieval >36 h after hCG injection. Although there is evidence to confirm the results, the results still need to be confirmed by large-sample, multicenter, randomized, controlled trials from other countries and regions.

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Conflicts of interest statement The authors declared no conflicts of interest related to this study.

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