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SPECIAL ARTICLE

Strategies to Reduce The Multifetal Pregnancy in Infertility Treatment

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During the past three decades, the modern infertility treatment has been worldwide successfully achieved to help tons of infertile couples to have their own babies. Since the birth of Louise Brown, the world's first in vitro fertilization (IVF) baby in 1978, there have been more than three million babies born from this technology all over the world[1]. It is estimated that about 1% of the baby born are from the assisted reproductive technology (ART). Coming up with the good success of the ART in the infertility treatment is the explosive of the huge multiple pregnancy rate compared to the natural conception, of which around 10% are high- order multiple pregnancy (HOMP)[2,3]. Recent report from European Society of Human Reproduction and Embryology (ESHRE) (generated from 32 European countries), the multiple pregnancy rate from ART has been consistently high at the figure of over 20% of the live birth[4]. In Thailand, The Royal Thai College of Obstetricians and Gynaecologists, reported that the twin pregnancy rate was 19.7% and the triplet and quadruplet were 1.9% and 0.5 % respectively during the past six years.

Multifetal pregnancy is well known as a high risk pregnancy. It associates with various maternal as well as neonatal morbidity and mortality. Multifetal pregnancy associates with life-threatening maternal morbidities, including pre-eclampsia, postpartum hemorrhage, gestational diabetes, preterm labor and preterm rupture of membranes. It is also associated with a five-fold increase risk of neonatal death, a four-fold increase in cerebral palsy and an eight-fold increase in low birthweight compared with singletons[5-7]. The risks are even higher in pregnancy with higher order of fetus. From a large study, including 316,696 twin, 12,193 triplet, and 778 quadruplet, had shown that triplet and quadruplet contained 1.5-2.2 times higher risk of maternal morbidity and 3-4 times of ≥1 infant death comparing with twin pregnancy[8]. These results confirmed that HOMP has significantly higher risks than twin pregnancies for most of maternal and neonatal complications. Apart from the health and social consequences on the families, these medical complications of multiple pregnancy are also present a significant financial burden including the antenatal surveillance, hospital cost and intensive neonatal care[9].

With all the risks and burdens consequence from the multifetal pregnancy, the strategies to reduce the high twin and HOMP rate arising from the modern infertility treatment are urgently required. How the multifetal pregnancy can be avoided without compromising the pregnancy rate is the most frequently asked question. Intrauterine insemination (IUI) and ART are the two most common infertility practices around the world. To achieve the goal of singleton healthy baby birth, the valid strategies for the multiple birth

reduction are needed to be implicated in the treatment protocol.

IUI has been widely used as a common method for infertility treatment. Base on the meta-analysis study, the combination of gonadotropin-induced control ovarian stimulation (COH) and IUI has been shown to result in significantly higher pregnancy rate as compare to IUI with natural cycle by the odds ratio of 1.6-2.0[10]. The rationale of COH is to increase the chance of pregnancy by induce multifollicular growth. However, this technique has a drawback effect by increasing the multifetal pregnancy rate as a result of many ovulating oocytes can get fertilized. How can we balance the chance of pregnancy with the risk of multifetal pregnancy in term of the ovulating follicle number? Recently, many strategies have been proposed to reduce the HOMP in the COH- IUI cycle with trivial impact on the pregnancy rate. Those strategies are:

- Start with the low dose gonadotropin to control ovarian stimulation (COH) and maintain the constant dose for 7-10 day before step up.
- Aim to obtain no more than two growing follicle in the insemination cycle. If there are three or more dominant follicles ≥16 mm., the cycle should either be cancel or reduce the supernumerary follicles by aspiration.

Ragni et al[11] reported their three -year experience of using low-dose recombinant follicle-stimulating hormone in 1,259 controlled-ovarian hyperstimulation and intrauterine insemination cycles. Fifty IU per day of recombinant follicular stimulating hormone (FSH) was commenced on day 3 and maintained until the size of the follicles reach ≥ 18 mm where human chorionic gonadotropin (hCG) was given and IUI was performed 34 hours later. The cycles should be canceled if three or more follicles ≥16 mm and/or five or more follicles ≥11 mm were detected. The mean number of follicles per patient was 2 follicles and the total number of canceled cycles was 132 cycles (10.5%). The clinical pregnancy rate per initiated cycle was 9.2% and the incidence of twins and high-order multiple pregnancies were 9.5% and 0%, respectively. On their review, ten studies started with the low dose gonadotropin and the mean clinical pregnancy rate was 11.1% while the incidence of HOMP was only 1%. The results were associated with a satisfactory pregnancy rate and a negligible risk of HOMP.

Dickey et al[12] has shown in their study that the risk factors for HOMP are the women's age, the number of follicles ≥10 mm and the treatment cycle. For the age of less than 32 years old, HOMP was 6% for three to six follicles and 20% for seven or more follicles. For the ages of 32 to 37 years old, HOMP was 5% for three to six follicles and 12% for seven or more follicles. In the first COH-IUI cycle, HOMP was 8% for three to six follicles and 15% for seven or more follicles. In the second cycle, HOMP did not occur unless there were more than six follicles. They proposed to withhold the hCG when there are seven or more preovulatory follicles of diameter ≥10 mm, which can significantly reduce the incidence of HOMP resulting from COH-IUI. The alternation of the cycle cancellation is supernumerary follicles aspiration if three or more follicles are larger than 16 mm. in order to reduce the follicle number to two. Reports from De Geyter et al[13] and Albano et al[14] have shown that the multifetal pregnancy could be prevented by supernumerary follicles aspiration without affecting the pregnancy rate.

For ART, twin and HOMP are still the bane of the treatment. The challenge currently faces practitioners of ART is to reduce the incidence of multifetal pregnancy without impacting on the pregnancy rate. Among the interventions aimed to achieve this goal is the reduction of the number of embryos transferred. It has been accepted that single embryo transfer is the most successful way to reduce the frequency of multiple pregnancies in IVF. There are many reports of single embryo transfer (SET) on day 2/3 with similar pregnancy rate to double embryo transfer[15-17]. Data suggested that extending embryo culture to Day 5/6 and transferring the embryo at the blastocyst stage would enhance the likelihood of pregnancy[18-19]. There are also more reports of single blastocyst transfer (SBT) with a high pregnancy rate[20-22]. However, most of reports on SET and SBT are only from the selected group of good prognosis infertile couples. They are young age, less than 38 years old, and have more than 4-6 good quality embryos on day 3. Various factors have impact on the

decision of the embryo number including the stage of embryo, the embryo score, age of the patient and the previous failed-IVF cycles. More studies are needed before the guideline can be established.

Data from few studies can answer some of these questions. Guerif et al[23] reported the comparison of SET on day 2 with SBT on day 5/6 in 478 young age couple (average 31-32 years old). They found that the SBT yielded a higher clinical pregnancy than the SET (29.6% vs 46.3% respectively) in the fresh transfer cycle. However, the subsequent frozen-thaw cycle, the SET group obtained a higher pregnancy rate per transfer which make the cumulative pregnancy rate of the combination of the fresh and frozen-thaw cycle similar in both the SET and SBT groups (34.2% vs 37.9%, respectively). This study did not observe any preference on the SET or SBT in term of delivery rate in the young age couples when combined the fresh and frozen-thaw cycle. Kula et al[24] compared the single with double blastocyst transfer (SBT vs DBT) in the two age groups, the young (25-37 years old) and the elderly groups (≥38 years old). In the young age group, both the SBT and DBT yielded the similar live birth rate (59% vs 60%, respectively) but the twin rate was much higher in DBT (47.6% vs 2.3%, respectively). In the frozen-thaw cycles, the cumulative live birth rate was higher in SBT group (72.8% vs 60.5%, respectively). In the elderly group, the DBT yielded a higher live birth rate than the SBT (43.3% vs 29.4%, respectively) with a comparable twin rate (36.4% vs 33.3%, respectively). The cumulative live birth combining fresh and frozen-thaw cycle was higher in DBT than SBT group (63.3% vs 28.6%, respectively). These results are in concerted with study by Mullin et al[25] where SBT and DBT were compared in the young age group of ≤40 years old. Similar clinical pregnancy rate (63% for SBT vs 61% for DBT) but significance of multiple pregnancy rate from (25% to 2%) was observed. These results demonstrate that for younger age group, single blastocyst transfer (SBT) is a better option in term of maintain the high pregnancy rate and minimize the multifetal pregnancy.

The guideline to reduce the multifetal pregnancy rate in IVF cycle should be:

- For young age group and good prognostic couples, SET on day 2/3 or SBT on day 5/6 should be the priority due to high cumulative pregnancy rate of combining fresh and frozen-thaw cycle and low the multiple pregnancy rate.
- DBT in young age group is not advised because there is no benefit on pregnancy rate and associates with much higher risk for multifetal pregnancy than SBT.
- For elderly couples, there is still not enough evidence, DBT in a fresh cycle is acceptable due to higher pregnancy rate than the combining of SBT in fresh and frozen-thaw cycle. However, the multiple pregnancy rate is still high. The couples should be informed about the risk for maternal and neonatal morbidity.
- There are not enough evidence to guide the number of the cleavage stage embryo for transferring in the elderly group, the poor prognosis group and the group with previous multiple IVF-failure.

Multifetal pregnancy reduction (MFPR) has been practice in some institutes for selective termination of the supernumerary fetus in the HOMP to improve the chance of survival and health of the remaining fetus. This procedure is an invasive technique, contains a moral dilemma. It should be considered as the last choice of all the strategies and associates with the pregnancy loss and prematurity.

In conclusion, the current impacts of the neonatal and maternal risks and burdens from multifetal pregnancy have been forcing the infertility providers to aware of the twin reduction and the high-order multiple pregnancy rate. In the countries where the infertility treatment is reimbursed by the public health system, the strategies for regulation of transferred embryo number can be instantly implicated. However, in the countries where the own-pay system, similar to Thailand, the regulation to control the number of embryo transferred and the multiple pregnancy rate may have to be waited.

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