

International Workshop for Junior Fellows :

1. Current status and problems of ART (assisted reproductive technology)

3) Current status and problems regarding assisted reproductive technology (ART) in Japan

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Against a background of improved education and social advancement of women, Japanese society is showing a trend toward delayed marriage and birth. The mean age at first birth was 25.7 years in 1975 and 30.3 years in 2012, increasing yearly. Furthermore, the total fertility rate was 1.43 in 2013, and remains well below the population replacement level (2.07). Reflecting these social conditions, there is a growing need for assisted reproduction technologies (ART), and the number of in vitro fertilization (IVF) cycles rose sharply from 1,195 in 1985, to 326,426 in 2012 (the largest number of IVF cycles in the world), making Japan a leading ART authority.

ART in Japan has the following features : 1) a high rate of frozen and thawed blastocyst transfer (FET) (36% of all treatment cycles, 73% of all ART births) ; 2) a high rate of ART indication for older women (40% of all cycles are over forty years old) ; 3) almost no ART using oocyte donation (OD) ; 4) a high rate (70% of all births) of single embryo transfer (SET) and a low rate (4%) of multiple pregnancy.

Despite the growing demand for ART in older women, there has been little progress in discussions about the advantages and disadvantages of OD, nor the development of legal systems ; creating a serious problem regarding ART in Japan. The only regulation concerning ART in Japan is the committee opinion of the Japan Society of Obstetrics & Gynecology (JSOG), and no action on legislation has been realized. There are many countries that legislate either for or against OD ; therefore, since Japan is a leading ART power, it is unusual that the country has no legislation regarding OD : legislation urgently needs to be considered.

Another problem concerns safety aspects for ART infants. It is known that ART babies have higher risks of preterm birth (PTB) and low birth weight (LBW). However, these risks are decreasing in Japan since SET strategies were adopted in 2008. Conversely, there are several studies showing that the mean birth weight after FET is significantly higher compared with fresh ET and all Japanese births. To explain these phenomena, epigenetics may play an important role. IVF children show different methylation levels and gene expressions both in imprinted and non-imprinted genes compared with children born from natural conception. Epigenetic modifications including DNA methylation is shown to affect fetal growth. From these studies, FET may modify epigenetics somehow, leading to imprinting disorders (e.g. Beckwith-Wiedemann Syndrome which seems to increase in ART children.) Further research

is needed such as long-term observational and comprehensive study.

Finally, we would like to introduce two leading research projects of new fertility treatment strategies in Japan. First, in vitro activation (IVA) : after collecting ovarian cortical tissues from primary ovarian insufficiency (POI) patients, the residual primordial follicles are activated and cultured in vitro, auto-grafted to the patient, and undergo IVF. Healthy live births after IVA have been reported recently. The second research project is to establish germ line cells from iPS cells. Gemmate production from germ cells derived from iPS cells in mice has been reported. This system may be available for humans in the future. These new strategies are feasible approaches to achievement of future pregnancy in women who are thought to be impossible to become pregnant, and further progress is desired for clinical application.
