Review Article

Assisted reproductive technology in China: compliance and non-compliance

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Abstract: According to the WHO, infertility and sterility will be the third-most serious disease worldwide in the 21st century, after cancer and cardiovascular diseases. In contrast to developed countries, assisted reproductive technology (ART) were not offered in China until the mid-1980s with the first in vitro fertilization (IVF) infant born in Taiwan in 1985, then Hong Kong in 1986, and mainland China in 1988, respectively. Since those inceptions, the practice of ART in China has evoked a variety of social, cultural, political and one-child policy responses that have resulted in restrictions on the number of IVF cycles performed annually. According to recent survey, an estimate 40-50 million women and 45 million men suffered from infertility, which is estimated that more than ten million Chinese infertile couples require ART treatment. However, it has limited access to ART facilities, many of them may not have a child are whirling to all types of fertility therapies. Exposure to radiation, pesticides and other environmental pollutants, work-related stress and unhealthy lifestyles are believed to contribute to the increasing incidence of infertility in China. The aim of this first report is to provide China nationwide ART data and government policy in compliance and non-compliance, particularly related to family plan policy in China.

Keywords: Assisted reproductive technology (ART); in vitro fertilization (IVF); infertility; policy; China

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According to the WHO, infertility and sterility will be the third-most serious disease worldwide in the 21st century, after cancer and cardiovascular diseases. Assisted reproductive technology (ART) refers to any procedure that involves either in vitro fertilization (IVF), surgically retrieving eggs from a woman's ovaries, fertilizing them with sperm in the laboratory, and returning the resulting embryo(s) to the woman's womb, or intrauterine insemination (IUI), non-surgically placing sperm inside a woman's uterus to facilitate fertilization. ART has evolved into the most effective fertility treatment presently available, stemming from an experimental method that resulted in the first birth in 1978 (1), to an estimated five million babies having been born over the last three decades (2,3). Approximately 1.5 million cycles of IVF are performed annually, resulting in the birth of 350,000 babies in worldwide (3). In contrast to developed countries, IVF was not offered in China until the mid-1980s with the first IVF infant born in Taiwan in 1985, then Hong Kong in 1986, and mainland China in 1988, respectively (4,5). Since those inceptions, the practice of ART in China has evoked a variety of social, cultural, legal, and ethical responses that have resulted in restrictions on the number of ART cycles performed annually. As a result, ART still remains

Figure 1 Mainland China assisted reproductive technology (ART) centers (the number) and sperm bank (SB) distributions [2011].

inaccessible to many infertile couples in China (6,7).

A recent epidemiology study concluded that 15% to 20% of the women of reproductive age in China suffer from infertility. That percentage translates into 40-50 million women, many of whom are demanding treatment, yet have limited access to ART facilities, especially in western area of China (*Figure 1*) (6-8). The study also estimated that 10-12% of men (45 million) suffer from male infertility, with a higher incidence of infertility in men residing in rural areas (15%) compared to their urban counterparts (10%) (6). Exposure to radiation, pesticides and other environmental pollutants as well as work-related stress and unhealthy lifestyles are believed to contribute to the increasing incidence of infertility in China (6-9).

Despite the "late" introduction of ART services to patients in China, ART centers are dedicated to providing their patients with all of the procedures that fall under the ART umbrella including artificial uterus insemination (IUI), in vitro maturation (IVM) of oocytes, oocytes cryopreservation, elective single embryo transfer (eSET), and blastocyst embryo transfer (bET), vitrification, preimplantation genetic diagnosis (PGD)/screening (PGS). In order to provide the best technologies in their ART centers, our colleagues in other countries have found that use of data collected through mandatory reporting may be used to develop evidence-based policies to further improve outcomes. Unlike the Centers for Disease Control and Prevention (CDC) report in the USA (7,10) and European IVF Monitoring (EIM) Program in Europe (11), ART clinics in China are not mandated to report their procedure outcomes. The aim of this report is to provide the country results of ART clinics since 1981 and its compliance/non-compliance in China conducted by the Chinese Society for Reproductive Medicine (CSRM).

Current status of China art

China's Ministry of Health (CMOH) by the end of 2011, had at least approved the organization of 178 reproductive centers and 13 sperm banks that are located in 30 provinces, autonomous regions and municipalities except Tibet (*Figure 1*). Official figures showed that as of end of 2012, China had

358 organizations authorized to conduct ART treatment.

According to our first-time nationwide survey of ART from current 178 reproductive centers and 13 sperm banks in China, data demonstrated that total ART cycle procedures of conventional IVF, ICSI, IVM, PGD, FET during1981-2004 were 78,002, 27,975, 726, 215 and 23,926, respectively; whereas the total ART cycle procedures of conventional IVF, ICSI, IVM, PGD, FET during 2005-2011were 393,538, 168,498, 2,596, 2,269, 124,501, respectively. As compared to above two periods, the pregnancy rate has been slightly increased, while the rates of miscarriage and ectopic have slightly decreased in second period. According to follow up survey for pregnancy and live births from 1981 through 2004, the cumulative birth defect rates from conventional IVF, ICSI and FET cycles were 1.08%, 1.27% and 0.86%, respectively; while the birth defect rates during 2005-2011 from conventional IVF, ICSI and FET cycles were 1.19%, 1.22% and 0.92%, respectively. As compared to two periods, there is no significant difference in all birth defect rates. In addition, total AIH/AID cycles during 2005-2011 were 192,020 with 15.94% clinical pregnancy rate, resulted in live birth of 24,308 infants with 0.61% birth defect. More recent report indicated that 124,468 IVF/ICSI cycles in China had the defect risk estimation of 1.37% compared with spontaneously conceived children (12). Multiple centers data analysis demonstrated that birth defect rates were 1.58% in ICSI and 1.11 in IVF from 15,405 ART offspring during year 2004-2008 (13). These results suggested that China shall effectively monitor ART procedures in order to further reduce patients' risk of multiple births and comply with one-child policy following ART.

Compliance of China regulation and policy

Regulation of ART in China

Regulation of ART has evolved in different ways in different countries (14). Some countries have issued laws aimed at controlling ART operation, while others have professional guidelines set by national scientific and medical societies (14). In 2001 the CMOH has issued four decrees (15), which included two methods—"Managerial Method for Human Assisted Reproduction", and "Managerial Method for Human Sperm Bank", and two technical standards—"Technical Standard for Human Assisted Reproduction", and "Technical Standard for Human Sperm Bank". These decrees require all assisted reproduction programs and sperm banks in China to be registered and monitored by the CMOH. In 2003, the methods and standards were amended and the amendments included incorporation of the "Ethical Principles for Human Assisted Reproduction and Sperm bank" into new regulations, called "Technical standards and Ethical Principles" (15). New CMOH regulations have required reproductive programs and sperm banks in China to be affiliated with authorized and permitted hospitals, virtually all of which are state run, they must comply with China's family planning policy, and thus the number of centers is limited by the government.

ART accessibility under regulation and policy

Bases upon CDC's 2010 Preliminary ART Success Rates, 154,417 ART cycles (excluding embryo banking cycles) were performed at 443 reporting clinics in the USA during 2010, resulting in 47,102 live births (deliveries of one or more living infants) and 61,561 infants (7,10). To put the disparity of ART service availability between the two countries into perspective, China has a more than four times population that of the USA (China, 1.34 *vs.* USA, 0.31 billion, 2011), leading to the number of ART centers per citizen to be 1 for every 700,000 people in the USA (443 centers, 2010) and 1 for every 7.5 million Chinese (178 centers, 2011). Even though expensive ART procedures without any medical insurance coverage, the ART cycles cost at an average cash of 30,000 Yuan (about $5,000), and the average cost of a live birth following fresh autologous cycles are 100,000 Yuan (about $16,666) or even more for an ART operation, demand still cannot be met, and many of infertile couples who may not have a child are whirling to all types of fertility therapies, and they are still on a waiting lists (7).

While the necessity for the provision of ART services in a country with such a large population may be questioned the "one child policy" implemented in 1979, has actually contributed to significantly decrease in birth rate (16,17). An increase in the rate of infertility where it is estimated that more than ten million Chinese infertile couples require ART procedures in order to conceive, has further contributes to a decline in the birth rate (7,18). One option to relieve rapidly increasing average age of the Chinese population and decline in birth rate would include relax the current complex "one-child policy" to a "two children policy" for "one-only-child couples" (i.e., couples in which one party was an only child) policy. Implementation of this policy change may lead to an increase in the number of Chinese couples seeking ART to overcome their infertility (19).

Requirement for personnel and facility

According to the new regulations, assisted reproductive programs or centers require a minimum of 12 medical staff [five board certified reproductive endocrinologists (RE) and one licensed urologist, three qualified laboratory personnel and three registered nurses] who have to be trained by one of ten CMOH-authorized reproductive training centers; facility space must be at least 260 m^2 and be equipped with specific equipment (15). Similarly, sperm bank must have a minimum of five medical staff (one board certified MD, one geneticist, two laboratory personnel and one managerial staff), at least 115 m^2 of facility space and meet the minimum equipment requirements, which is China specials (15).

Patient care regulations

Patients undergoing ART treatment must provide three certificates-personal ID, marriage certificate and birth permitted certificate with the aim of complying China "one-child policy" family plan (15), and physicians must obtain their informed consent for the procedure as well. The provision of ART services to patients with mental disease, acute infection in urological and reproductive system, sexually transmitted disease, serious genetic disease by "China law of mother and infant health care", addition to drugs, exposure to teratogenic radiation, toxicant and drugs is forbidden. Furthermore, ART services are not be provided to women who cannot carry a pregnancy due to a uterine or other factors. Gender selection, surrogacy, use of a gestational carrier, compensation for donated gametes, directed gamete donation, embryo donation, cytoplasmic and nuclear transfer, use of hybridized gamete and transferring non-human gamete and embryos to human body also are prohibited. Up to three embryos may be transferred to women ≥35 years of age and no more than two embryos may be transferred to women under 35. Gamete donors must be anonymous, not compensated and are limited to no more than five recipients, which is similar to USA (15).

The only source of donor oocytes is from IVF patients who have superfluous oocytes and willing to donate their oocytes to other patients. These IVF patients must be treated as anonymous donors and are required to undergo a physical examination, blood testing. Additionally, the gametes or resulting embryos must be quarantined for six months prior to transfer to the recipient. Sperm donor must be between 22 and 45 years old, Chinese origin, and be unrelated to the recipient's family. Similar to oocyte donors, sperm donors must undergo a physical exam, serologic and genetic testing and the samples must be quarantined for a minimum of six months, which is similar to USA. Fresh semen samples cannot be directly used for donor recipient. Donors are assured privacy protection. Laboratory quality control and long term record keeping are essential (15).

Inspection and accreditation for compliance

The CMOH is authorized to conduct on-site initial inspections and rechecked inspections of institutions in their jurisdictions for every two years according to quality standard guidelines and policy regulations. The important parts of quantity standard guidelines and policies included to complying CMOH regulation, limited performing 1,000 IVF cycles per center/year, no less than 95% in following up rate after IVF-ET birth, minimum fertilization rates of 65% following conventional IVF and 70% after intracytoplasmic sperm injection (ICSI), no less than 15% of pregnancy rate at first year and no lower than 20% thereafter, at least 10% frozen embryo transfer (FET) cycles resulting in clinical pregnancies, a minimum 15% pregnancy rate in AIH/AID cycles, evidence that efforts are made to minimize the risk of multiple pregnancy, avoided twins and prohibited triplets, etc. (15). Any major deficiency or violation may result in license revocation for at least two years. In 2007, the CMOH transferred the authority and responsibility to inspect these facilities to local agencies including the department of health in provinces, autonomous regions and municipalities. Local authorities were instructed to conduct thorough inspections, rigorously review new applications and strictly control the number of institutions authorized for assisted reproductive technologies even though no official number to be announced.

The CSRM under the Chinese Medical Association (CMA) was established in 2005; subsequently, multiple sub-societies of reproductive medicine were organized in provinces, autonomous regions and municipalities. Their major functions are to guide China assisted reproduction, help the CMOH and local health authority's management, develop technology and research, train new medical staff and incorporate cooperation with international reproductive societies or associations, such as ASRM, ESHRE and ASPIRE.

No-compliance with regulation and policy

In December 2011, the country's controversial policy banning gestational carriers in the assisted reproduction

fell under the international spotlight when the "eight-baby scandal" was reported in the southern city of Guangzhou, where a wealthy couple emerged paid nearly one million Yuan ($160,320) to have eight babies (four boys and four girls) simultaneously, by using IVF and two surrogates (7). This was particularly challenging, because use of gestational carriers is illegal in Mainland China. In the Hong Kong Special Administrative Region of China, the commercialization of surrogate motherhood and non-genetic surrogacy (in cases of homosexuals, single parents and unmarried individuals) are banned. The regulation is based on the fact that the intended parents will have to adopt the child within six months after live birth and that the birth mother cannot be forced to give up the child (20). There are some European countries in which surrogacy is legal. In the UK, surrogacy is legal but the law stipulates that any form of commercial surrogacy is prohibited. Also in the USA, some States have friendly policy for surrogacy. In India and Thailand, the commercial surrogacy is also legal (21). All these are made on the characteristics of their countries and citizens situation and the possible consequences to their society. So, surrogacy is the most complicated part in ART (21). The Chinese Ministry of Health (CMOH) also prohibits buying and selling of gametes, zygotes and embryos (15). However, there are signs that some institutions, tempted by huge financial rewards, perform ART procedures that are not in compliance with CMOH regulations. The evidence of non-compliance includes reports of more than 25,000 children born through gestational carriers in China over the past three decades, with their births arranged by over 500 unlicensed agencies and advertisements from more than 100 agencies online provide evidence to validate suspicions of non-compliance (22). Estimates of up to a 30% increase in the number of these procedures in the past two years suggest that the demand for gestational carriers is growing (22). The factors that contribute to the increased demand for gestational carriers are not limited to infertility. Many Chinese want to have a baby during the auspicious and the luckiest lunar year of the dragon of 2012, as the creature is associated with might, intelligence and is historically linked to emperors. While the CMOH requires that the use of reproduction techniques such as IVF must comply with China's family planning policy (15), affluent individuals who are not necessarily infertile or unable to carry a pregnancy, use gestational carriers to bypass the one-child rule, because IVF may create a higher chance of having twins or even triplets, thus twins and other multiple-birth deliveries are exempt from the penalties for violation of the one child policy (22,23). Even though there is no specific law prohibiting the use of gestational carriers in China, in 2001 this practice was driven underground when the CMOH banned trade in fertilized eggs and embryos, forbidding hospitals from performing embryo transfer to gestational carriers (23).

The robust China economy has given many wealthy couples, both infertile and fertile options of building their families through ART. One favorable option of coming to U.S. ART clinics for gestation carriers, fulfilling their dream of having a baby and the baby, by birthright, is entitled to U.S. citizenship (24). A gestational surrogacy typically costs $80,000 to $120,000, with higher costs if there are complications or if repeated implants are needed. Most Chinese couples insist on eggs from ethnic Chinese women, which further drives up the cost. Chinese donors typically are paid up to $15,000, as compared to a Caucasian donor, which is typically $5,000 to $8,000. Additional premiums are usually paid to Chinese donor if she has perfect SAT scores, is very attractive, or if she went to a prestigious school, now Chinese egg donor is in great demand as the premiums (24).

Faced with rising demand for ART procedures in China, the CMOH has recently proposed that it would grant licenses to clinics owned and operated by qualified, private individuals (7). With such a large amount of unsatisfied demand, the opportunity for modernized ART centers in China is huge, and the private clinic or hospital will now be able to access this market as well (7). However, this proposal has suddenly frozen in February, 2013, since CMOH launched a campaign to fight against ART abuse (25). All unauthorized ART use, surrogate motherhood and the illegal collection and supply of sperm and eggs, as well as the illegal sale and abuse of ovulation induction medicine, will be targeted (25). CMOH also ordered all of their local branches to suspend authorizations for new organizations that wish to offer ART treatments, as well as launched an overhaul for ART treatments that are being offered at authorized institutions (25).

Future perspective

For future perspective, here are some constructive suggestions for China ART development: (I) we strongly suggest that all reproductive center or fertility clinics in China shall be required to report their success rates annually to China health authority, such as Chinese Center for Disease Control and Prevention (China CDC), like the

United Sates of American and Europe EIM (10,11). In this way, China health authority could effectively monitor ART procedures and its risk for elucidating their destabilizing and generative impacts as they make their way around the nation; (II) CMOH and local health authority should continue to consider opening more reproductive centers under strictly guideline and regulation in order to improve the availability of ART services to infertile Chinese couples; (III) CMOH may consider inclusion of the infertility treatment under medical insurance coverage for eligible Chinese couples; (IV) CSRM should cooperate with CMOH and local health authority to license new reproductive centers, generate the inspection checklists, create new guidelines and practice consents, and engage technical monitoring as well; (V) Reproduction centers should optimize their techniques to use mini-stimulation protocols and select perfect the single embryo transfer (sSET) in order to further reduce patients' risk of multiple births following ART and comply to the "one child policy" as well. This effort would also be supported if the "one child policy" is relaxed and couples who have a successful cycle, have the option of transferring cryopreserved embryo(s) in a future cycle; (VI) IVF laboratories shall be independently accredited by China health authority, and adhere to strict requirements to perform quality control and quality assurance for all the contact materials or micro- environmental conditions, and participate in proficiency testing, in order to reduce the potential risks associated with ART manipulations.

While, the practice of ART is not legislated in China today, it is highly regulated for its compliance. It is our hope that the regulation will continue to evolve as advances occur and efforts will be made to increase the number of reproductive centers, in order to satisfy dramatic demanding in ART treatment in China. In addition, it must be recognized that we may never be able to practice a 'perfect ART'. Debate will continue to see the over the same foundation of evidence both for and against the use of ART; those who see promise, safety and efficiency in ART will forever be spurned by others who believe that the treated individuals are under increased risks. At the end of the day, though, we are all making efforts to do what is safe and effective for our patients under regulation; continued progress will require research, standardization of procedures and incorporation of evidence-based protocol.

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