ORIGINAL

Survey on the incidence of multiple pregnancies and neonatal outcomes by fertility treatment in Tokushima Prefecture, Japan

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Abstract : A survey on the incidence of multiple pregnancies and neonatal outcomes by assisted reproductive technology (ART) and non-ART fertility treatments was performed in 2011 and 2021. Questionnaires were sent to all institutions with obstetrics and gynecology departments in Tokushima Prefecture, Japan, to collect data on fertility treatments and neonatal outcomes in 2011 and 2021. Non-ART fertility treatments were classified into ovarian stimulation (treatments for cases without ovulation disorder) and ovulation induction (treatments for cases with ovulation disorder). Among all pregnancies, the multiple pregnancy rates in 2011 were 7.7% for ovarian stimulation, 5.5% for ovulation induction, and 8.4% for ART, whereas those in 2021 were 3.8%, 2.3%, and 1.9%, respectively. The rates of triplet pregnancies in 2011 were 0.85% for ovulation induction, 2.4% for ovulation induction, and 1.4% for ART, whereas those in 2021 were 0% for all treatments. The rates of low birth weight, admission to a neonatal intensive care unit, and neonatal death in 2011 were 53.8%, 9.61%, and 9.61%, respectively, whereas those in 2021 were 40.9%, 22.7%, and 0%, respectively. These findings indicate that rates of multiple pregnancies, including higher-order multiple pregnancies, by fertility treatment have decreased over the last 10 years in Tokushima Prefecture. However, some adverse neonatal outcomes have still occurred. J. Med. Invest. 71 : 251-253, August, 2024

Keywords **:** *ART, ovarian stimulation, ovulation induction, multiple pregnancy*

INTRODUCTION

The number of fertility treatment cycles, including ovarian stimulation, ovulation induction, and assisted reproductive technology (ART) such as in vitro fertilization/intra cytoplasmic sperm injection, has been increasing yearly in Japan (1). For instance, Japan has been reported to be one of the largest users of ART worldwide in terms of the annual total number of treatment cycles performed (2).

On the other hand, in accordance with the fact that infertility treatments have been generalized, the incidence of multiple pregnancies, including triplet, quadruplet, or more (higher-order multiple pregnancies) due to multiple ovulation and multiple embryo transfer increased remarkably during the late 1980s to the early 2000s. Multiple pregnancies, especially higher-order multiple pregnancies, can lead to an increased risk of health issues for both mothers and babies (3-9), and can also induce social problems such as mental and economic burdens among patients and their families (9).

To help prevent multiple pregnancies in ART, in 1996, the Japan Society of Obstetrics and Gynecology (JSOG) recommended that the number of transferred embryos should be limited to three or fewer, and then a maximum of one or two in 2006. Subsequently, the incidence of multiple pregnancies by ART drastically decreased, from about 20% in the early 1990s to 3.0% in 2021 (1). JSOG has been collecting ART data through a nationwide registry system since 1986, and as a result, trends in the incidence of multiple pregnancies by ART are now more fully understood (1, 10). On the other hand, no such registry system has been established for non-ART fertility treatments (e.g., ovarian stimulation, ovarian induction), and thus, the incidence of multiple pregnancies remains unknown. Therefore, in the present study, to confirm the current status and related issues and evaluate changes over the last 10 years, we conducted a survey on the incidence of multiple pregnancies in ART and non-ART fertility treatments in 2011 and 2021. We also collected data on the neonatal outcomes of multiple pregnancies to confirm their effects on the health risk to infants.

Received for publication April 4, 2024 ; accepted April 17, 2024.

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MATERIALS AND METHODS

Questionnaires were sent to all institutions with an obstetrics and gynecology department in Tokushima Prefecture (39 institutes in 2012 and 34 in 2022), Japan, in November 2012 and November 2022 to collect data on fertility treatments for the previous year (i.e., 2011 and 2021) and their neonatal outcomes.

The number of fertility treatment cycles, including ovarian stimulation (non-ART medical treatments for cases without ovulation disorder), ovulation induction (non-ART medical treatments for cases with ovulation disorder) and ART, the total number of pregnancies by each treatment, the total numbers of multiple and higher-order multiple pregnancies, birth weight, and neonatal outcomes were collected.

This study was approved by the institutional clinical research review board of Tokushima University (No. 3994-1). All information was disclosed in an information disclosure document at Tokushima University Hospital HP.

RESULTS

Of the 39 and 34 participating institutions, responses were obtained from 22 (56.4%) and 25 (73.5%) in 2012 and 2022, respectively. Because all institutions providing fertility treatments responded, this survey collected almost all of the relevant data in Tokushima Prefecture.

Among all pregnancies, the multiple pregnancy rates in 2011 were 7.7% for ovarian stimulation, 5.5% for ovulation induction, and 8.4% for ART, whereas those in 2021 were 3.8%, 2.3%, and 1.9%, respectively (Table 1). The rates of triplet pregnancies in 2011 were 0.85% for ovulation induction, 2.4% for ovulation induction, and 1.4% for ART, whereas those in 2021 were 0% for all treatments. No quadruple or higher-order multiple pregnancies were reported in either 2011 or 2021.

The low birth weight, admission to a neonatal intensive care unit (NICU), and neonatal death rates in 2011 were 53.8%, 9.61%, and 9.61%, respectively, whereas those in 2021 were 40.9%, 22.7%, and 0%, respectively (Table 2).

DISCUSSION

The results of the present survey revealed that the incidence of multiple pregnancies by fertility treatment in Tokushima Prefecture, Japan, have decreased in the past decade. As noted above, the multiple pregnancy rates by ART drastically decreased after the JSOG recommendation (1, 10). An annual report on the Japan ART registry system showed that the multiple pregnancy rates in 2011 and 2021 were 4.1% and 3.0%, respectively (1, 11). A similar trend was seen for ART in Tokushima Prefecture ; namely, the multiple pregnancy rates in 2011 and 2021 were 8.4% and 0%, respectively. These data indicate that most institutes, including those in Tokushima Prefecture, have been following the JSOG recommendation, which has led to a reduction in multiple pregnancy rates by ART. On the contrary, ART recently began to be covered by Japan's universal health insurance system and the number of embryo transfers covered by insurance is up three to six times per child bearer. Thus, multiple embryo transfer, i.e., double embryo transfer, could be increased in cases with recurrent implantation failure, leading to another increase in the multiple pregnancy rate, which would pose more health risks for both mothers and infants.

As noted above, because no registry systems have been established for non-ART fertility treatments, the multiple pregnancy rates in recent years for ovarian stimulation and induction remain unclear. The present findings revealed that the multiple pregnancy rates for ovarian stimulation were 7.7% and 3.3% in 2011 and 2021, respectively, while those for ovulation induction were 5.5% and 2.3%, respectively. These findings indicate that the multiple pregnancy rate for non-ART fertility treatments had also decreased in recent years. Such trends might be due to the establishment of safer stimulation protocols and the proposal of cancellation criteria for human chorionic gonadotropin (hCG) injections in cases involving multiple follicular growth (12).

Studies published in the late 1990s and early 2000s have shown that higher-order multiple pregnancies were higher in non-ART than in ART fertility treatments (13-15). This is because in ART, the number of transferred embryos can be restricted, whereas in non-ART stimulation with multiple follicular growth, all large follicles are ovulated after hCG injection. It has been reported that obstetric, perinatal, and neonatal

Table 1. Clinical outcomes in each infertility treatment

	2011				2021			
	Cycles, *n*	Pregnancies, *n*	Multiple pregnancy, *n (%)*	Higher-order multiple pregnancies, *n (%)*	Cycles, *n*	Pregnancies, *n*	Multiple pregnancy, *n (%)*	Higher-order multiple pregnancies, *n (%)*
Ovarian Stimulation	1048	117	9 (7.7%)	1 (0.85%)	1294	104	4 (3.8%)	0 (0.0%)
Ovulation Induction	1498	127	7 (5.5%)	3 (2.4%)	1429	133	3 (2.3%)	0 (0.0%)
ART	716	179	15 (8.4%)	2 (5.6%)	1451	423	8 (1.9%)	0 (0.0%)
Total	–	423	31 (7.3%)	6 (1.4%)	–	660	15 (2.3%)	0 (0.0%)

ART ; assisted reproductive technology, Cycle number of ART ; total number of embryo transfer ; % of multiple and triplet pregnancy ; number of multiple pregnancies / total number of pregnancies.

Table 2. Neonatal outcomes of multiple pregnancies in each infertility treatment

	2011 (n = 52)	2021 (n = 22)
Low birth weight	28 (53.8%)	9 (40.9%)
Extremely low birth weight	2 (9.61%)	0 (0.0%)
Admission to NICU	17 (32.7%)	5 (22.7%)
Neonatal death	2 (9.61%)	0 (0.0%)
Some complications	0 (0.0%)	0 (0.0%)

Cases of known outcomes are included. Low birth weight ; weight at birth of < 2500 g, extremely low birth weight ; weight at birth of < 1000 g, NICU ; neonatal intensive care unit.

complications are more prevalent in triplets and higher-order multiple pregnancies than in twins (3-9). To help avoid these risks, reduction surgery has been performed worldwide since the mid-1980s, and improvements in obstetric, perinatal, and neonatal outcomes after this surgery have been reported (16-18). However, several ethical, legal, and psychological problems associated with these methods remain in various countries, including Japan (19-22). On the contrary, in the present survey, the triplet pregnancy rates for ovarian stimulation and induction were lower than those for ART in 2011, and no higher-order multiple pregnancies were achieved in 2021. Thus, compliance with the JSOG recommendation for ART and the safer protocol and cancellation criteria for non-ART fertility treatments may play important roles in the prevention of higher-order multiple pregnancies.

In the present survey, adverse neonatal outcomes such as low birth weight and admission to an NICU were confirmed in both 2011 and 2021 ; however, no extremely low birth weight or neonatal death outcomes were observed in 2021. One possibility for these outcomes is that triplet pregnancies were achieved in 2011, but not in 2021, and thus, neonatal outcomes may have been worse in 2011. However, because the source of each neonatal outcome could not be evaluated in this survey, the true cause remains unknown. Further evaluations that can specify the causes of adverse neonatal outcomes are needed to help prevent health issues in babies conceived by fertility treatment.

In summary, the results of the present survey indicated that the multiple pregnancy rates, including higher-order multiple pregnancies, may have decreased over the last 10 years in Tokushima Prefecture. On the contrary, some adverse neonatal outcomes have still been seen in multiple pregnancies achieved by ART and non-ART fertility treatments. Thus, the JSOG recommendation for embryo transfer should be followed and safer protocols for non-ART fertility treatments should be established.

CONFLICTS OF INTEREST

The authors declare that no conflicts of interest exist.

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