Obstetric outcomes and congenital abnormalities in infants conceived with oocytes matured in vitro

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Today a key component to infertility treatment with in vitro fertilization (IVF) is controlled ovarian hyper-stimulation (COH), a process whereby supra-physiological amounts of exogenous gonadotropins are administered for the purpose of inducing multi-follicular growth. It is generally accepted that the number of mature oocytes retrieved relates to the number of embryos available for transfer which in turn correlates with the likelihood of treatment success. However, side effects of COH (short and possibly long-term) continue to raise concerns (van Leeuwen et al., 2011). Robert Edwards, the pioneer of IVF believed that recovery of immature oocytes followed by in vitro maturation (IVM) would be one of the potentially useful treatments for women with infertility (Edwards, 2007a,b). IVM of immature eggs has emerged as a gonadotropin-independent treatment alternative to conventional IVF (Chian et al., 2004; 2013). IVM differs from conventional IVF treatment in two major ways. First is the absence of COH and second is the collection of immature oocytes that are cultured in vitro until they reach the metaphase II (mature) stage before IVF is performed.

Since the introduction of IVF and other assisted reproductive technologies (ARTs) for infertility treatment, the health of infants born from these techniques has been a major concern. Individual studies have examined the birth weight and major defects in infants born from IVF or other ART procedures, but with conflicting results (Hansen, 2002; Schieve LA et al., 2002; Rimm et al., 2004; Davies et al., 2012).

Table I. — List of centers contributing to present data and numbers of IVM infants provided by the end of 2010 from each clinic (center).

Country and clinics (centers)	Number of IVM babies reported
Australia • Fertility Specialists WA, Bethesda Hospital, 25 Queenslea Drive, Claremont WA 6010, Australia	19
Brazil • Nilo Frantz Human Reproduction and Research Center, Nilo Pecanha Avenue 1221, 10th Floor, Porto Alegre, RS, Brazil	15
Canada • McGill Reproductive Center, McGill University Health Center (MUHC), 687 Pine Avenue W, Montreal, Quebec, Canada, H3A 1A1	132
China • Medical Center for Human Reproduction, Dept. of Obstetrics and Gynecology, Peking University Third Hospital, Beijing, China. 100191 • Center for Reproductive Medicine, The First Affiliated Hospital with Nanjing Medical University, Nanjing, 210029	292

Table I. — Continuation.

Country and clinics (centers)	Number of IVM babies reported
• Center for Reproductive Medicine, The First Affiliated Hospital of Anhui Medical University, Hefei, 230022 • Reproductive Medicine Center, The First Affiliated Hospital of Wenzhou Medical College, Wenzhou, 325000 • Reproductive Medical Center, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, 510700 • The Women's Clinic and IVF Center, The Hong Kong Sanatorium and Hospital	
Columbia • CECOLFES, Bogota	7
Denmark • The Fertility Clinics, Herlev University Hospital, DK-2730, Herlev	34
Finland • Infertility Clinic, The Family Federation of Finland, Helsinki	52
France • Service de Gynecologie-Obstetrique et Medicine de la Reproduction, Hospital Antoine Beclere, Clamart, France; • Laboratoire de Biologie de la Reproduction-IFREARES, 20 Route de Revel, 31400-Toulouse	50
Greece • IAKENTRO, 4 Ag, Vasiliou St, Thessaloniki	1
Israel • IVF Unit, Assaf Harofeh Medical Center, Tel-Aviv University, Zerifin	3
Italy • Biogenesi Reproductive Medicine Centre, Istituti Clinici Zucchi, V Zucchi, 24-Monza	157
Japan • IVF Namba Clinic and IVF Osaka Clinic, Osaka • Yoshida Ladies' Clinic, Sendai • Kyono ART Clinic, Sendai	69
Jordan • ART and Genetic Department, AL-Khalidi Medical Center	1
Norway • Bioingeniør, Fertilitetssenteret ved Aleris Sykehus, Fredrik Stangs gt. 11-13, O264 Oslo	4
South Korea • Maria Fertility Hospital, Seoul	455
Slovenia • Department of Reproductive Medicine and Gynecologycal Endocrinology, University Clinical Centre Maribor	7
Sweden • Fertility Unit, Karolinska Institutet, Department of Clinical Science, Technology and Intervention, Karolinska University Hospital, Novum, SE 14186 Stockholm	22
Taiwan • IVF Unit, Department of Obstetrics and Gynecology, Shin Kong Wu Ho-Su Memorial Hospital, Taipei	20
Turkey • IVF Unit, Department of Obstetrics and Gynecology, Dokuz Eylul University, Izmir • Gurgan Clinic Women Health, Infertility and IVF Center, Cankaya Caddesi, No.20/3, Ankara	8
United Kingdom • Oxford Fertility Unit, Level 4, Womens Centre, John Radcliffe Hospital, Oxford, UK OX3 9DU	8
United States of America • Delaware valley Institute of Fertility and Genetics, Marlton, NJ08053	6
Vietnam • HCM Society for Reproductive Medicine (HOSREM), 84T/8 Tran Dinh Xu Street, District 1, Ho Chi Minh City	59
Total	**1,421**

Table II. — Obstetric outcomes and congenital abnormalities in 1,421 IVM babies born from 1,187 pregnancies.

Characteristics from 1,187 pregnancies	**Singleton pregnancies (n = 960)**	**Twin gestation pregnancies (n = 221)**	**Triplet gestation pregnancies (n = 5)**	**Quadruplet gestation pregnancies (n = 1)**
Mean gestational age at delivery (weeks + days)	37 + 4	36 + 5	35 + 2	29 + 0
No. of deliveries at > 37 weeks (%)	855 (89)	60 (27)	0 (0)	0 (0)
No. of deliveries at 34-37 weeks (%)	82 (9)	132 (60)	5 (100)	0 (0)
No. of deliveries at < 34 weeks (%)	23 (2)	29 (13)	0 (0)	1 (100)
Total of 1,421 newborns	**Singleton newborns (n = 960)**	**Twin newborns (n = 442)**	**Triplet newborns (n = 15)**	**Quadruplet newborns (n = 4)**
Birth weight (mean ± SD) (g)	2,965 ± 532	2,434 ± 365	1,968 ± 472	1,330 ± 84
No. of LBW (%)	35 (4)	59 (13)	12 (80)	0 (0)
No. of VLBW (%)	5 (1)	12 (3)	2 (13)	4 (100)
Median Apgar score at 1 min (inter-quartile range)	9 (7-9)	8 (7-9)	8 (8-9)	–
No. of Apgar score at 1 min less than 7 (%)	133 (14)	31 (14)	0 (0)	–
Median Apgar score at 5 min (inter-quartile range)	10 (9-10)	10 (9-10)	8 (8-9)	–
No. of Apgar score at 5 min less than 7 (%)	25 (3)	5 (2)	0 (0)	–
Incidence of congenital anomalies (%)	15 (2)	3 (1)	0 (0)	0 (0)

LBW: Low birth weight, 1,500-2,500 g;
VLBW: Very low birth weight, < 1,500 g;
SD: Standard deviation.

the infants born after IVM (Söderström-Anttila et al., 2006; Buckett et al., 2007; Fadini et al., 2012). In this paper we describe 1,421 IVM babies born from 1,187 pregnancies from 31 IVF clinics located in 22 countries (Table I). Data was collected at the time of birth and includes stillbirths but not pregnancy terminations. Information on maternal age, mode of delivery, multiple pregnancy, gestational age at delivery, birth weight, Apgar scores, and congenital abnormality are presented. Congenital malformations were recorded based on the International Statistical Classification of Diseases and Related Health Problems 10th Revision (WHO, 2007).

The mean maternal age was 34 years. Forty percent (n = 476) infants were delivered vaginally and 60% (n = 711) were delivered by caesarean section. Mean gestational age at delivery and mean birth weight of all infants in singleton, twin, triplet and quadruplet are shown in Table II. Of the 1,421 IVM infants born, there were 18 major congenital abnormalities. It is comparable with the prevalence of major birth defects (MBD) with the spontaneous conception per birth ranged to International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR, 2011).

This is the largest report of infants born from IVM to date. A study is planned to analyse the prevalence of major birth defects in infants conceived following IVM treatment compared to outcomes of this IVM cohort with similar populations of infants conceived by conventional IVF. Based on our preliminary data, IVM does not appear to pose any significantly increased risk of poor obstetric outcomes or congenital abnormalities over those already accepted with IVF or other ARTs.

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