

Retrospective analysis of neonates born after assisted reproductive technology and admitted to the neonatal intensive care unit

Dear Editor,

There are limited studies evaluating neonatal outcomes after assisted reproductive technology (ART) in Asia, especially Southeast Asia, hence this study aimed to fill this gap in literature. We conducted a retrospective study on a group of neonates conceived via ART performed at the National University Hospital (NUH), Singapore and admitted to its neonatal intensive care unit (NICU), over a 5-year period from January 2013 to December 2017 to evaluate the immediate neonatal outcomes after ART.

Six hundred and thirty-nine babies were conceived via ART in NUH and born in NUH during the period, of whom 102 were admitted to NICU. The characteristics are represented in Table 1. Thirty-seven (5.8%) were born at less than 35 weeks gestation, with majority of them (25/37, 67.6%) associated with multiple births. Of the 639 babies, 41 (6.4%) were of low birth weight (<2kg); and 35 of these low-weight babies were associated with multiple births. Of the whole cohort, 34 (5.3%) were small for gestational age.

Majority of the NICU-admitted neonates were products of multiples (66, or 65% versus 35% singletons). Sixty were from twins and 6 from triplets. The mean gestational age and birth weight of multiples was 34.6 ± 2.4 weeks and 2052 ± 506 g, compared to 35.1 ± 3.9 weeks and 2387 ± 854 g in the singletons, respectively. Gestational age was similar but weight was significantly lighter for the multiples compared to singletons ($P=0.01$).

Top reasons for admission to NICU were: low birth weight of less than 2kg (41), less than 35 weeks gestation (37) and respiratory distress syndrome (RDS) (25). Sixteen of these neonates were admitted for the aforementioned reasons, with 11 of them products of multiples.

Twenty-four, or 3.8% of the study cohort had major congenital anomalies, giving an incidence of 37.6 per 1,000 ART live births. The overall incidence of congenital anomalies for all births in NUH during the 5-year period was 17.3 per 1,000 live births (334/19,325). Fifteen of these neonates in the study cohort were products of multiples. One third of these neonates had 2 or more systems affected, while the rest had a single system affected.

The overall median length of stay for neonates admitted to the NICU was 10.5 (interquartile range [IQR] 5–21)

days. The median length of stay in multiples was 12 (IQR 7–19.3) vs 8.5 (IQR 5–25.8) days in singletons ($P=0.89$). The twin with the congenital anomaly stayed significantly longer—31 days (IQR 12–58) compared with the other twin without any congenital anomaly—16 days (IQR 4–43) ($P<0.01$).

Neonates born with congenital anomalies were more likely to die ($P<0.001$) than those born without congenital anomalies. There were 3 in-hospital deaths (3/639), giving an incidence of 4.69 deaths per 1,000 ART birth conceived and delivered in NUH. This is in contrast to the overall mortality rate in NUH for all births in NUH over the 5-year period, which was 1.6 deaths per 1,000 births (30/19,325) (chi-square 10.5, $P<0.05$). Prematurity and congenital anomalies contributed to all deaths in the ART-conceived neonates admitted to NICU.

Major neonatal morbidities after ART in our study included prematurity from multiple births, and its attendant complications of low birth weight, growth retardation and RDS requiring mechanical ventilation. There was a relatively long duration of hospitalisation of 1 month on average for pre-term multiples with congenital malformations.

Our findings concur with international studies that multiplicity from ART pregnancies correlates with a high prevalence of pre-term births and its attendant complications of prematurity.¹⁻³

Singapore's national infant mortality rate is 2.1 deaths per 1,000 live births.⁴ In our study cohort, we estimated this to be 3.8 to 4.7 per 1,000 live births conceived via ART. The high prevalence of prematurity and congenital malformations in our ART-conceived cohort with multiple births may have contributed to the higher infant mortality rate observed. However, it is important to recognise that in addition to ART processes, adverse neonatal outcomes may also result from underlying subfertility.⁵

Since 2011, the Ministry of Health (MOH), Singapore has mandated that the maximum number of embryo transfers be limited to 2 at any one time, with only exceptional cases allowing 3.⁶ The impact of the implementation of this policy on the rates of prematurity and multiplicity has not yet been determined. We suggest single embryo transfer (SET) be mandated by legislation and policy in couples with better prognosis. Fortunately,

Table 1. Characteristics of the cohort admitted to NICU

Characteristics	n=102
Ethnicity,^a no. (%)	
Chinese	51 (50.0)
Indian	22 (21.6)
Malay	16 (15.7)
Of other Southeast Asian descent (Vietnamese, Filipino)	4 (3.9)
Caucasian	9 (8.8)
Total of Asian descent	93 (91.2)
Maternal age,^a mean±SD, years	
Overall	35.0±3.7
Range	28–47
Gestational age,^a mean±SD, weeks	
Overall	34.8±3.0
Range	27–41
Multiples	34.6±2.4
Singletons	35.1±3.9
Neonates <35 weeks n=37	33.8±2.7
Neonates <28 weeks n=4	26.3±1.0
Birth weight,^a mean±SD, g	
Overall	2170±666
Range	750–4190
Multiples	2052±506
Singletons	2387±854
Neonates <35 weeks	1985±547
Terms	2808±655
Parity,^a no. (%)	
Multiples	66 (64.7)
Twins	60 (58.8)
Triplets	6 (9.1)
Singletons	36 (35.3)
Congenital anomalies,^b no. (%)	
Multiples	15 (2.3)
Singletons	9 (1.4)
Total	24 (3.8)

Table 1. Characteristics of the cohort admitted to NICU (Cont'd)

Characteristics	n=102		
Reasons for admission to NICU, ^b no. (%)			
	Total N=639	Multiples n=66	Singletons n=36
Low birth weight <2kg	41 (6.4)	31 (46.9)	10 (27.8)
Prematurity <35 weeks	37 (5.8)	25 (37.9)	12 (33.3)
Respiratory distress syndrome	25 (3.9)	18 (27.3)	7 (19.4)
Hypoglycaemia requiring intravenous drip	30 (4.7)	22 (33.3)	8 (22.2)

NICU: neonatal intensive care unit

^a 102 babies were admitted to NICU.^b 639 is the study cohort, i.e. the total number of babies conceived via assisted reproductive technology at the National University Hospital and born in the hospital. Data on the babies not admitted to NICU were not available due to confidentiality issues. The numbers do not add up to 100% as each baby may have more than 1 reason for admission.

Singapore has facilities to freeze embryos, which encourage elective SET (eSET) over multiple transfers, while also reducing procedures and costs.

At our centre, we advocate eSET, which is in tandem with a review of the National ART Surveillance System data done in the US. The review concluded that substantial reduction of ART-related multiple births could be achieved by single-blastocyst transfers among favourable and average prognosis patients less than 35 years old.⁷ A Singapore study by KK Women's and Children's Hospital In Vitro Fertilisation Centre similarly concluded that single-blastocyst transfers confer lower multiple pregnancy rates and should be offered as standard practice where possible.⁸ Currently, only a third of our patients undergo eSET and only 1 embryo is transferred for first-time patients below 35 years old. Women above 35 years old are encouraged to transfer only 1 embryo. From 2017 to 2019, our eSET rate ranged from 21.8 to 37.1%. In 2017 to 2018, we encountered only 1 case after eSET where the embryo split after transfer, resulting in twins. Our centre's total clinical pregnancy rate (included fresh, thawed and ≥1 embryo transfer) was 32.3 to 38.4% from 2017 to 2019. The multiple pregnancy rate for 2017 to 2018 was 10.5%. Hence, we advocate eSET to avoid complications arising from multiple births.

At a national level, outcomes of ART-conceived pregnancies should be available for audit by the Agency for Care Effectiveness, MOH Singapore. Lack of national audit data of neonatal outcomes makes it

difficult to determine the true healthcare costs of these fertility treatments.

We encourage all countries to set up robust ART registries to enable better tracking of neonatal outcomes after ART. Pre- and antenatal counselling of couples considering ART,⁹ and redefining obstetric practices—including rigorous patient selection, procedural techniques and limiting the number of embryo transfers—are crucial. Public healthcare budgeting and provisions of tertiary neonatal intensive care and specialised paediatric centres should also move in tandem with the observed trend of increasing ART usage.

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