

Why does mode of conception affect early breast-feeding outcomes? A retrospective cohort study

Shiue-Shan Weng

National Yang Ming University

Li-Yin Chien

National Yang Ming University

Min Chang (✉ R004872@ms.skh.org.tw)

Shin Kong WHS Memorial Hospital

Research Article

Keywords: assisted reproductive technology, infertility, breastfeeding, causal mediation analysis, conception

Posted Date: December 17th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-125572/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Abstract

Background: Women who conceived through Assisted Reproductive Technology (ART) may experience poorer breast-feeding outcomes compared to women who conceived naturally; nevertheless, the mechanism of this relationship has not been explored. This study aimed to examine the effect of mode of conception on breast-feeding outcomes during the first two months postpartum and identify the potential pathways for this relationship.

Methods: A retrospective cohort study was conducted in a sample of 5,474 women with live births using hospital administrative data from January 2014 through December 2018. Participants were classified by mode of conception as follows: fertile women who conceived naturally (fertile women; $n=4,363$), women with infertility who conceived naturally (sub-fertile women; $n=706$), and women with infertility who conceived through ART (women with infertility; $n=405$). The patterns of infant feeding were acquired at hospital discharge, the first week, the first month, and the second month postpartum. Binary and multinomial logistic regression and causal mediation analyses were performed.

Results: Infertile and sub-fertile women had 34% (95% CI 1.03, 1.73) and 60% (95% CI 1.11, 2.31) increased risks of introducing formula prior to the first week postpartum, respectively, and 31% (95% CI 1.01, 1.70) and 59% (95% CI 1.10, 2.31) higher risks of exclusive breastfeeding for less than one week during the first two months postpartum, respectively, compared to fertile women. The relationships were mediated through delivery complications, multiple gestations, preterm delivery, low birth weight, and admission to neonatal/paediatric intensive care units (NICU/PICU). The path with the highest proportion mediated was through multiple gestations (60.47% for infertile women) and admission to NICU/PICU (68.60-72.61%). The effect of mode of conception on breastfeeding outcomes was not significant in cases of no maternal and infant morbidities.

Conclusions: During the first two months postpartum, infertile and sub-fertile women both had short duration (<7 days) of exclusive breastfeeding and introduction of formula prior to the first week postpartum. The relationships were mainly mediated through multiple gestations and admission to NICU/PICU. Designing programmes to reduce adverse maternal and infant health events, like a single embryo transfer policy, is suggested to improve perinatal outcomes, together with the following breast-feeding outcomes.

Background

The rates of childbirth resulting from Assisted Reproductive Technology (ART) are increasing worldwide;^[1] however, pregnancies resulting from ART are also at higher risks for adverse birth outcomes (e.g. preterm birth and low birthweight).^[2–4] Continuous breastfeeding may aid growth and development in children conceived through ART because human breastmilk contains unique nutrients that promote neuronal, intestinal, and immunological development. Nonetheless, women who conceived through ART have distinctive features that might diminish their ability to breastfeed, such as the following: experiencing a great sense of sadness and anxiety after the diagnosis of infertility; carrying a psychological burden about the unpredictability of ART-related procedures; experiencing increased anxiety about early parenting difficulties; and being at higher risks for adverse birth outcomes.^[2, 4–9]

There are studies demonstrating that women who conceived through ART cease breastfeeding earlier or breastfeed for shorter durations than those who conceived naturally; however, contrary findings indicate no such association.^{10–14} This inconsistency may owe to study limitations, including lack of appropriate comparison groups, insufficient sample sizes, and failure to control the effects of characteristics of the setting where women go for prenatal visits or to give birth.^[10–15] Additionally, a study showed that professional support to prolong breastfeeding is the most effective during the first two months postpartum;^[16] still, most studies assessed outcomes at only one point during the first two months. Hence, they could not determine the timing of the emergence of breastfeeding differences.

Additionally, if an association exists, a systematic exploration of the potential pathways between the mode of conception and early breast-feeding outcomes has yet to be conducted. Understanding such potential pathways may be useful to provide evidence-based strategies to improve breastfeeding. Previous studies show that women who conceived through ART are at a higher risk for pregnancy/delivery complications,^[2–4] and such experiences and treatments could delay breast fullness owing to elevated stress hormones.^[17] Pregnancies resulting from ART are also at higher risk for low birthweight, preterm birth, and admission to neonatal/paediatric intensive care units (NICU/PICU).^[2, 4, 6] Babies with poor health status often experience difficulty in latching, which results in ineffective suckling.^[18] This can negatively influence mothers' perception on the adequacy of their milk production.^[19] Furthermore, considering that multiple births are more prevalent among mothers who conceived through ART, some may experience increased care burden and subsequently increased difficulty to establish sufficient milk supply for the infants.^[20] Hence, in this study, the potential mediators—pregnancy and delivery complications—were considered in the pathway of maternal health factors; the potential mediators—multiple gestation, low birthweight, preterm birth, and admission to NICUs/PICUs— were considered in the pathway of infant health factors.

Methods

Aim, design, and setting of the study

This study aimed to examine the effect of mode of conception on breast-feeding outcomes during the first two months postpartum and to identify and quantify how much of the effects are mediated through maternal and infant health factors. (Fig. 1)

A retrospective cohort study was conducted. The source population was women who had live births in a medical centre in northern Taiwan from January 2014 to December 2018. The reason for choosing this period is that the national surveys indicate similar breast-feeding rates at the first and second month postpartum during this period of time; [21] this choice could thereby reduce differences caused by time trends or other unmeasured factors. The participating medical centre is in northern Taiwan; has an infertility clinic and a department of Obstetrics; and received, two decades ago, the implementation of a Baby-Friendly Hospital Initiative (BFHI), which ensures that all postpartum women receive similar prenatal care and breast-feeding counselling. Generally, the BFHI complies with the “Ten Steps to Successful Breastfeeding” framework, developed by the WHO and UNICEF. [22] We assessed the source population’s exposure status from January 1999 (i.e. the current electronic medical records system was initiated), and participants were followed up until the second month postpartum.

The data were compiled from medical records, birth registrations, medical materials and examinations systems, and breast-feeding follow-up records. Breast-feeding follow-up records were kept by trained nurses who identified breast-feeding outcomes through face-to-face interviews during hospital stays and telephone interviews; these were conducted at one week, one month, and two months postpartum, and they had been incorporated into nursing routines since the implementation of the BFHI.

An experienced obstetrician and an epidemiologist with experience in study design and analysis using medical records and birth certification databases scrutinized the measurements of each variable to achieve face validity of the data.

Participants

There were 8,830 women with live births, 3,356 of whom were excluded. The exclusion criteria were: age under 20 years ($n = 43$), fewer than five prenatal visits ($n = 863$), infants with congenital defects ($n = 48$), unmarried status ($n = 265$), insurance status below low income ($n = 1$), and probable fertility treatment outside the hospital ($n = 2,091$), which were identified through those who delivered by a certain obstetrician who admitted most patients from an outside infertility clinic. Mothers with fewer than five prenatal visits were excluded to ensure that the participants received similar breast-feeding consultation from conception to breast feeding; unmarried mothers were excluded because the Assisted Reproduction Act (ARA) allows ART only for married couples. Women who conceived through intrauterine insemination ($n = 45$) were also excluded because this procedure is not defined as ART. [23]

After the four follow-ups it was noticed that, 19.62% ($n = 1,074$) of the participants were unable to follow-up because they refused to be interviewed during hospital stays or did not answer phone calls after hospital discharge; still, 80.38% ($n = 4,400$) of our sample completed the four follow-up waves. After multiple imputation to handle missing values on breast-feeding outcomes ($n = 1,074$) and employment ($n = 931$), 5,474 participants were included in the data analysis (Fig. 2).

Exposure

By mode of conception, participants were categorised into three groups: fertile women who conceived naturally; women with infertility who conceived naturally (i.e. sub-fertile women); and women with infertility who conceived through ART (i.e. women with infertility). Infertility was defined as the failure to achieve a clinical pregnancy after more than 12 months of regular unprotected sexual intercourse and being identified with an infertility diagnosis (i.e. International Classification of Diseases (ICD)-9 628.0 to 628.9 or ICD-10 N97.0 to N97.9) through medical records. Women with no infertility diagnosis and no history of ART were defined as fertile women. ART conception was defined as cases in which a woman received implantation ≤ 22 days after her last menstrual period (i.e. child’s birth date minus their gestational age). The value of 22 days was determined by the calculation of gestational age–14 days adding 5 days (to account for 3–5 days in embryo culture)–[24] and 3 days of error. [25] Women who were diagnosed with infertility but had no history of ART or for whom the date of implantation was not within the last menstrual period adding 22 days (whichever met) were classified as sub-fertile women.

Outcomes

Timing of breast-feeding initiation, formula introduction, and breast-feeding discontinuation

The patterns of infant feeding included exclusive and mixed breastfeeding and formula feeding; these were assessed at hospital discharge (i.e. less than the first week postpartum), first week, first month, and second month postpartum. Timing of breast-feeding initiation was divided into before or after the first week postpartum because most women initiated breastfeeding before hospital discharge. Timing of formula introduction was defined as the first-time introduction of formula during the follow-up period, and it was classified into five groups: less than a week, one week, one month, two months after birth, and no formula introduction within two months postpartum. Breast-feeding discontinuation was defined as discontinuation of breastfeeding during the follow-up period and was classified into five groups: less than a week, one week, one month, two months after birth, and no breast-feeding discontinuation within two months postpartum.

Duration of exclusive breastfeeding

Infant breast-feeding practice intervals were converted into days and summed to compute the duration of exclusive breastfeeding; this allowed for us to identify changes in infant feeding practices (e.g. from formula feeding to exclusive breastfeeding). Exclusive breastfeeding indicated that the infant received only breast milk, without any other liquids/solids. As only a small proportion of participants (6.0%) exclusively breastfed for one week to less than one month, the durations from one week to less than one month and from one month to less than two months were merged into one category. Therefore, the duration of exclusive breastfeeding was categorised into four groups: less than one week, one week, one week to less than two months, and two months.

Confounders

Based on previous studies and the assumption of a possible underlying mechanism, we tested for the minimally sufficient adjustment set of confounders using a causal directed acyclic graph created with DAGitty (see Additional file 1); this served to avoid the risk of over-adjustment or inappropriate adjustment for mediators.[26, 27] The following confounders were included in the final models: maternal age, maternal occupational status, abortion history, parity, and pre-existing diseases.

Potential Mediators

As shown in Fig. 2, two mediating pathways were examined—maternal health and infant health. Maternal health factors included pregnancy complications (i.e. gestational diabetes mellitus, oligohydramnios, gestational hypertension, and pre-eclampsia) and delivery complications (i.e. premature rupture of membranes, abruptio placentae, placenta praevia, postpartum haemorrhage, prolonged labour, obstructed labour, malpresentation, and prolapsed umbilical cord), data for which were obtained from birth registrations. Infant health factors included multiple gestation, low birthweight (< 2,500 g), preterm birth (< 37 weeks), and admission to NICU/PICU.

Statistical analysis

All statistical tests were performed using STATA version 15.0.[28] Maternal and infant characteristics were described using counts and percentages by mode of conception, and we compared these characteristics among groups using linear regression for continuous variables and binary logistic regression for dichotomous variables. To estimate odds ratios (ORs), relative risk ratios (RRRs), and 95% confidence intervals (CIs) for the association between mode of conception and breast-feeding outcomes during first two months postpartum adjusting for the confounders, binary and multinomial logistic regressions were used as well. The reference group consisted of fertile women. All *P*-values were two-tailed with a significance level of 5%.

To identify the mediating pathways through maternal and child health factors, causal mediation analysis was conducted. The criteria for a mediator were examined by binary or multinomial logistic regression as follows: (1) a model for mediator, conditional on mode of conception and confounders; and (2) a model for breast-feeding outcomes, conditional on mode of conception, the mediator, and the same confounders.[29] To test *a priori* the theorised mechanisms, only mediators of interest that met the criteria were entered into the causal mediation analysis performed with the *paramed* command.[29] The total effects of mode of conception on breast-feeding outcomes were divided into (1) effects exerted through mediators (natural indirect effect, NIE); and (2) effects not exerted through mediators (natural direct effect, NDE). The odds ratios of NIE and NDE (OR^{NIE} and OR^{NDE}) were obtained through the *paramed* program. The proportion mediated was calculated as $[(OR^{NDE} \times (OR^{NIE} - 1)) / (OR^{NDE} \times OR^{NIE} - 1)] \times 100\%$ to interpret the proportion of the total effect explained by the mediation.

Missing data

There was no significant difference for mode of conception and confounders between women who had missing data and women who had complete data (data not shown). To reduce potential bias, missing data on employment ($n = 931$, 17.01%) and breast-feeding practices ($n = 1,074$, 19.62%) were handled by the multivariate imputation by chained equations (MICE) method [30]. Twenty imputations were used to reduce the sampling error, and Rubin's combination rules were used to consolidate the obtained estimates.[31]

Sensitivity analyses

An analysis for women who did not have adverse maternal or infant health conditions was conducted to further examine whether the difference in breast-feeding practices persisted between the mode of conception.

Results

Maternal and infant characteristics by mode of conception

Among the 5,474 participants, 4,363 (79.7%) were fertile, 706 (12.9%) were sub-fertile, and 405 (7.4%) were women with infertility conceived through ART. The maternal and infant characteristics by mode of conception are presented in Table 1. Both sub-fertile and women with infertility were more likely to be older, primiparous, and to have a history of abortion and pre-existing diseases than fertile women. Women with infertility

were less likely to be employed compared with fertile women. Regarding maternal and infant health conditions, and compared with fertile, sub-fertile women and women with infertility were more likely to have delivery complication, multiple gestation, low birthweight, preterm birth, and admission to NICU/PICU. However, sub-fertile women and women with infertility had a similar risk for pregnancy complications compared with the fertile women.

Table 1

Maternal and infant characteristics by mode of conception (N = 5,474)

Characteristics	Fertile women (n = 4,363)	Sub-fertile women (n = 706)	P-value	Women with infertility (n = 405)	P-value
Maternal age, mean ± SD	32.78 ± 0.07	35.13 ± 0.15	< 0.01	36.60 ± 0.17	< 0.01
Employment status, n (%)					
Unemployed	1322 (30.30)	215 (30.45)	0.92	158 (39.01)	< 0.01
Part-time job/full-time job	3041 (69.70)	491 (69.55)		247 (61.00)	
Parity, n (%)			< 0.01		< 0.01
1	2426 (55.60)	458 (64.87)		287 (70.86)	
≥ 2	1937 (44.40)	248 (35.13)		118 (29.14)	
Abortion history, n (%)			< 0.01		0.03
No	2774 (63.58)	401 (56.80)		236 (58.27)	
Yes	1589 (36.42)	305 (43.20)		169 (41.73)	
Pre-existing diseases, n (%)			< 0.01		< 0.01
No	3941 (90.33)	543 (76.91)		330 (81.48)	
Yes	422 (9.67)	163 (23.09)		75 (18.52)	
Pregnancy complications, n (%)			0.06		0.26
No	4216 (96.63)	672 (95.18)		387 (95.56)	
Yes	147 (3.37)	34 (4.82)		18 (4.44)	
Delivery complications, n (%)			< 0.01		< 0.01
No	3140 (71.97)	445 (63.03)		213 (52.59)	
Yes	1223 (28.03)	261 (36.97)		192 (47.41)	
Multiple gestation, n (%)			< 0.01		< 0.01
No	4324 (99.11)	659 (93.34)		331 (81.73)	
Yes	39 (0.89)	47 (6.66)		74 (18.27)	
Low birth weight, n (%)			< 0.01		< 0.01
No	4110 (94.20)	638 (90.37)		335 (82.72)	
Yes	253 (5.80)	68 (9.63)		70 (17.28)	
Preterm birth, n (%)			0.01		< 0.01
No	4146 (95.03)	633 (89.67)		338 (83.46)	
Yes	217 (4.97)	73 (10.34)		67 (16.54)	
Admission to NICU/PICU, n (%)			< 0.01		< 0.01
No	3797 (87.03)	560 (79.32)		303 (74.81)	
Yes	566 (12.97)	146 (20.68)		102 (25.19)	

Note. P-values were computed using linear regression for continuous response variables and binary logistic regression for dichotomous response variables. The reference group consisted of fertile women. ART, assisted reproductive technology; NICU/PICU, neonatal intensive care unit/paediatric intensive care unit; SD, standard deviation.

Association Between Mode Of Conception And Early Breast-feeding Outcomes

Both sub-fertile women and women with infertility were more likely to introduce formula before the first week postpartum than fertile women by 34% (adjusted RRR = 1.34, 95% CI = 1.03, 1.73) and 60% (adjusted RRR = 1.60, 95% CI = 1.11, 2.31), respectively. Additionally, both sub-fertile women and women with infertility had a higher risk of exclusive breastfeeding for less than seven days compared with fertile women by 31%

(adjusted RRR = 1.31, 95% CI = 1.01, 1.70) and 59% (adjusted RRR = 1.59, 95% CI = 1.10, 2.31), respectively. Neither timing of breastfeeding initiation nor of breastfeeding discontinuation was associated with mode of conception (Table 2).

Table 2

Association between mode of conception and early breast-feeding outcomes (N = 5,474)

Early breast-feeding outcomes	n	(%)	Mode of conception (ref.= Fertile women)			
			Sub-fertile women		Women with infertility	
			Adjusted RRR	(95% CI)	Adjusted RRR	(95% CI)
Timing of breast-feeding initiation						
≤ 1 week	5366	(98.03)	1.00	(Reference)	1.00	(Reference)
> 1 week	108	(1.97)	0.85 ^a	(0.46, 1.60)	1.20 ^a	(0.60, 2.43)
Timing of introduction of formula						
No formula introduction	958	(17.50)	1.00	(Reference)	1.00	(Reference)
<1 week postpartum	3250	(59.37)	1.34	(1.03, 1.73)*	1.60	(1.11, 2.31)*
1st week postpartum	404	(7.38)	1.26	(0.85, 1.86)	1.01	(0.57, 1.79)
1st month postpartum	774	(14.14)	0.87	(0.61, 1.24)	0.91	(0.56, 1.47)
2nd month postpartum	88	(1.61)	1.44	(0.73, 2.84)	0.30	(0.04, 2.31)
Timing of discontinuing any breast feeding						
No breast-feeding discontinuation	4265	(77.91)	1.00	(Reference)	1.00	(Reference)
<1 week postpartum	106	(1.94)	0.85	(0.45, 1.59)	1.25	(0.62, 2.52)
1st week postpartum	71	(1.29)	1.78	(0.98, 3.23)	0.94	(0.36, 2.45)
1st month postpartum	418	(7.64)	0.94	(0.68, 1.31)	1.10	(0.73, 1.68)
2nd month postpartum	614	(11.22)	0.99	(0.76, 1.29)	1.16	(0.83, 1.63)
Duration of exclusive breast feeding						
2 months	852	(15.56)	1.00	(Reference)	1.00	(Reference)
<1 week	2652	(48.45)	1.31	(1.01, 1.70)*	1.59	(1.10, 2.31)*
1 week	824	(15.05)	0.87	(0.64, 1.24)	0.76	(0.46, 1.24)
>1 week to < 2 months	1146	(20.94)	1.28	(0.95, 1.71)	1.31	(0.86, 1.98)
<i>Note.</i> Adjusted relative risk ratios were estimated using multinomial logistic regression, except for timing of breast-feeding initiation presenting as odds ratios using binary logistic regression, after adjusting for maternal age, maternal occupational status, abortion history, parity, and pre-existing diseases.						
^a Adjusted odds ratios; * $P < .05$; RRR, relative risk ratios; <i>ref.</i> , reference group; ART, assisted reproductive technology; CI, confidence interval.						

Causal mediation analyses

All mediators of interest in the hypothesised model met the mediator criteria (see Additional file 2) and were included in the causal mediation analysis, except for pregnancy complications. The pathways between mode of conception and introducing formula before the first week postpartum and exclusive breastfeeding for less than one week are presented in Table 3.

The pathway between sub-fertile women and the introduction of formula before one week postpartum was mediated by delivery complications, of which the proportion mediated accounted for 13.88%. Larger proportions of mediation were through infant health factors including multiple gestations (25.56%), low birth weight (14.77%), preterm birth (24.24%), and admission to NICU/PICU (70.95%). The proportion mediated of the total effect of sub-fertile women on less than a week of exclusive breast feeding, which was similar to that for the effect of on the introduction of

formula before one week postpartum, was 14.16% for delivery complications, 25.56% for multiple gestation, 18.60% for low birth weight, 24.77% for preterm birth, and 70.95% for admission to NICU/PICU.

The pathway between women with infertility and the introduction of formula before one week postpartum was mediated by delivery complications, of which the proportion mediated accounted for 27.88%. Infant health factors including multiple gestation (60.47%), low birth weight (29.21%), preterm birth (37.07%), and admission to NICU/PICU (68.60%) also explained larger proportions mediated. The proportion mediated of the relationship between women with infertility and exclusive breast feeding for less than one week was 24.66% through delivery complications, 60.47% through multiple gestations, 28.20% through low birth weight, 35.39% through preterm birth, and 72.61% through admission to NICU/PICU.

Table 3

Causal mediation analysis: effect of mode of conception on breast-feeding outcomes through mediators

Mediators	Effect of sub-fertile women on introduction of formula at ≤ 1st week postpartum			Effect of women with infertility on introduction of formula at ≤ 1st week postpartum			Effect of sub-fertile women on exclusive breast feeding for less than one week			Effect of women with infertility on exclusive breast feeding for less than one week		
	OR ^{NDE}	OR ^{NIE}	PM%	OR ^{NDE}	OR ^{NIE}	PM%	OR ^{NDE}	OR ^{NIE}	PM%	OR ^{NDE}	OR ^{NIE}	PM%
Maternal health pathways												
Delivery complications	1.33**	1.04**	13.88	1.45**	1.12**	27.88	1.32**	1.04**	14.16	1.44**	1.10**	24.66
Infant health pathways												
Multiple gestation	1.03**	1.01**	25.56	1.02**	1.03**	60.47	1.03**	1.01**	25.56	1.02**	1.03**	60.47
Low birth weight	1.30**	1.04**	14.77	1.46**	1.13**	29.21	1.28**	1.05**	18.60	1.44**	1.12**	28.20
Preterm birth	1.28**	1.07**	24.24	1.44**	1.18**	37.07	1.27**	1.07**	24.77	1.45**	1.17**	35.39
Admission to NICU/PICU	1.19**	1.39**	70.95	1.37**	1.59**	68.60	1.19**	1.39**	70.95	1.28**	1.58**	72.61
<p><i>Note.</i> Mediators of interest that did not meet the mediator criteria are not shown. All models were adjusted for confounders-maternal age, maternal occupational status, abortion history, parity, and pre-existing diseases. ** $P < .001$; ART, assisted reproductive technology; OR^{NDE}, odds ratios of natural direct effect; OR^{NIE}, odds ratios of natural indirect effect; PM, proportion mediated; NICU/PICU, neonatal intensive care unit/paediatric intensive care unit. Reference group for mode of conception was fertile women. Reference group for timing of introduction of formula was no formula introduction within two months postpartum. Reference group for duration of exclusive breast feeding was two months.</p>												

Sensitivity analysis

Among mothers who experienced no adverse maternal or infant health conditions, the effect of mode of conception on the timing of formula introduction and exclusive breastfeeding duration among sub-fertile women and women with infertility was no different from that in fertile women, after accounting for the same confounders (Table 4).

Table 4

Association between mode of conception and early breast-feeding outcomes in women without adverse maternal and infant health conditions (N = 3,161)

Early breast-feeding outcomes	n (%)	Mode of conception (ref.= Fertile women)			
		Sub-fertile women		Women with infertility	
		Adjusted relative risk ratios	(95% CI)	Adjusted relative risk ratios	(95% CI)
Timing of introduction of formula					
No formula introduction)	740 (23.41)	1.00	(Reference)	1.00	(Reference)
< 1 week postpartum	1422 (45.00)	1.08	(0.79, 1.47)	1.36	(0.84, 2.18)
1st week postpartum	318 (10.06)	1.15	(0.74, 1.79)	0.84	(0.42, 1.71)
1st month postpartum	612 (19.36)	0.73	(0.48, 1.11)	0.85	(0.48, 1.53)
2nd month postpartum	69 (2.18)	1.49	(0.70, 3.17)	0.40	(0.05, 3.09)
Duration of exclusive breast feeding					
2 months	656 (20.75)	1.00	(Reference)	1.00	(Reference)
< 1 week	1235 (39.07)	1.04	(0.76, 1.43)	1.19	(0.73, 1.92)
1 week	654 (20.69)	0.72	(0.49, 1.06)	0.73	(0.40, 1.31)
> 1 week to < 2 months	616 (19.49)	1.10	(0.76, 1.58)	1.32	(0.77, 2.27)
<i>Note.</i> ART, assisted reproductive technology; CI, confidence interval; ref., reference group; Adjusted relative risk ratios were adjusted for maternal age, maternal occupational status, abortion history, parity, and pre-existing diseases.					

Discussion

These results suggest that during the first two months postpartum, both sub-fertile women and women with infertility had a shorter duration of exclusive breastfeeding (i.e. less than one week) and an earlier introduction of formula (i.e. before the first week postpartum), but did not cease breastfeeding early. The causal mediations between these relationships were consistent with our hypothesised model, including delivery complications, multiple gestation, low birthweight, preterm birth, and admission to NICU/PICU. The paths with the highest proportion mediated were through multiple gestations and admission to NICU/PICU. Additionally, the effect of infertility on poor early breast-feeding outcomes disappeared when women who had maternal and infant health conditions were excluded.

Our findings echo those of a previous study, which suggested that women who undergo ART exclusively breastfeed for a shorter duration compared with fertile women.[10] Furthermore, we found that they were more likely having the early introduction of formula rather than the complete cessation of breastfeeding. An earlier introduction of formula could lead to insufficient milk production, which increases in severity over time, and thereby results in a shorter exclusive breast-feeding duration.

This study further found that the differences in the timing of formula introduction between modes of conception occurred before the first week postpartum; in other words, the earliest difference occurred while mothers and infants were still in the hospital. These differences occurred in the hospital owing to women with infertility having experienced more adverse maternal and infant health conditions during hospitalization. Breast-feeding intention is a strong predictor of breast-feeding initiation.[32] Hence, the finding of similar rates of breast-feeding initiation and discontinuation across modes of conception supports our following assumption: that sub-fertile women and women with infertility intended to breastfeed, but experienced difficulties in the early postpartum period that forced them to introduce formula earlier than preferred, leading to a shorter duration of exclusive breastfeeding.

This study demonstrated that multiple gestation serves as an important mediator in the relationship between women with infertility and early breast-feeding outcomes; it explained approximately 60.47% of the proportion mediated. In Taiwan, the ARA allows for the implantation of fewer than five embryos at a time.[33] However, transferring multiple embryos during ART is a well-documented risk factor for multiple gestations and subsequent risks for low birthweight and preterm. Therefore, the introduction of a single embryo transfer policy is suggested to improve perinatal outcomes, together with the following breast-feeding outcomes.

Preterm birth, low birthweight, and multiple gestations are all known risk factors for NICU/PICU admission; hence, approximately 70% of the proportion mediated that was explained by admission to NICU/PICU owed partially to the correlation between the mediators and certain paths between the mediators (i.e. that could result in the indirect effect being counted at least twice in the mediation analysis).[34] However, this highlights the importance of the NICU/PICU; therefore, targeting both sub-fertile women and women with infertility and developing a lactation support programme in the NICU/PICU is important. This remark becomes especially relevant if we consider the increased number of births resulting from ART.[35]

Moreover, our findings on the fact that certain sub-fertility and women with infertility (i.e. who did not face any adverse maternal and infant health outcomes) had early breast-feeding outcomes like those for fertile women allow for an inference; that the difference in breast-feeding behaviours between modes of conception owed to medical exclusion, as these interfered with breast-feeding practices. However, not all medical exclusions are necessary. For example, two studies remarked the occurrence of unnecessary NICU admissions in recent years.[36, 37] Thus, to reduce unnecessary NICU admission, the need to scrutinize and loosen the NICU admission criteria was suggested; doing so may thereby decrease adverse breast-feeding events resulted from unnecessary NICU admission.

Strengths Of The Study

We investigated the relationship between mode of conception—as categorised into three groups—and early breast-feeding outcomes during the first two months postpartum, a topic that has been sub-optimally approached in the literature. Previous studies have not examined whether sub-fertile women and women with infertility displayed different effects regarding early breast-feeding outcomes. Moreover, our assessment took place across multiple time points, allowing for the investigation on the emergence of breastfeeding differences. Additionally, we identified the maternal and infant health pathways using formal causal mediation analysis to provide evidence-based strategies to improve breastfeeding.

Limitations

First, our results were based on data from a single hospital; thus, the generalizability of our findings are limited. Second, given that this was a retrospective cohort study, data collection was restricted to past medical records; thus, our study lacked information on staffs' and family members' recommendations and behaviours regarding birth complications, all of which may influence breastfeeding behaviour. Third, our causal mediation models assumed parallel mediation; this was because a sequential causal mediation software for multiple categorical mediators, which could be used to identify numerous specific pathway effects when a correlation between mediators exists, was not available.[38]

Conclusion

Sub-fertile women and women with infertility were more likely to introduce formula before the first week postpartum and have an exclusive breast-feeding duration of less than one week during the first two months than fertile women. The poorer breast-feeding outcomes mainly owed to adverse maternal and infant health conditions (i.e. delivery complications, low birthweight, multiple gestations, preterm birth, and admission to NICU/PICU) among women with infertility. Targeting and designing programs to reduce those mediators, especially multiple gestations and admission to NICU/PICU, could diminish the difference in breastfeeding between mode of conception.

Abbreviations

ART: Assisted reproductive technology

NICU/PICU: Neonatal intensive care units or paediatric intensive care units

BFHI: Baby-Friendly Hospital Initiative

ARA: Assisted Reproduction Act

Declarations

Ethics approval and consent to participate:

This study was approved by the institutional ethics review board of Shin Kong Wu Ho-Su Memorial Hospital (NO. 20190402R) and performed in accordance with the Declaration of Helsinki and the relevant regulations. This study was a retrospective analysis of administrative data and met the criteria for waiving informed consent in the minimal risk study; therefore, the exemption for informed consent was granted by the institutional ethics review board of Shin Kong Wu Ho-Su Memorial Hospital. Patient identity was masked by anonymization and by transcoding their unique identification numbers into different strings.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding:

This study was supported by funding from Shin Kong Wu Ho-Su Memorial Hospital (NO. 107GB006). The funders played no role in the study design, analysis, or the reporting of results.

Authors' contributions

SSW: Project development, data collection, data analysis, manuscript writing. LYC: Project development, manuscript editing. MC: Project development, managed data collection, manuscript editing. All of the authors reviewed and approved the final draft.

Acknowledgments:

The authors would like to thank Dr. Sheng-Hsuan Lin for his helpful advice on the causal mediation analysis.

References

1. Dyer S, Chambers GM, de Mouzon J, Nygren KG, Zegers-Hochschild F, Mansour R, Ishihara O, Banker M, Adamson GD: **International Committee for Monitoring Assisted Reproductive Technologies world report: Assisted Reproductive Technology 2008, 2009 and 2010†.** *Human Reproduction* 2016, **31**(7):1588-1609.
2. Jackson RA, Gibson KA, Wu YW, Croughan MS: **Perinatal outcomes in singletons following in vitro fertilization: a meta-analysis.** *Obstetrics and gynecology* 2004, **103**(3):551-563.
3. Pandey S, Shetty A, Hamilton M, Bhattacharya S, Maheshwari A: **Obstetric and perinatal outcomes in singleton pregnancies resulting from IVF/ICSI: a systematic review and meta-analysis.** *Human reproduction update* 2012, **18**(5):485-503.
4. Qin J, Liu X, Sheng X, Wang H, Gao S: **Assisted reproductive technology and the risk of pregnancy-related complications and adverse pregnancy outcomes in singleton pregnancies: a meta-analysis of cohort studies.** *Fertility and sterility* 2016, **105**(1):73-85.e71-76.
5. Hammarberg K, Fisher JR, Wynter KH: **Psychological and social aspects of pregnancy, childbirth and early parenting after assisted conception: a systematic review.** *Human reproduction update* 2008, **14**(5):395-414.
6. Allen VM, Wilson RD, Cheung A, Wilson RD, Allen VM, Blight C, Désilets VA, Gagnon A, Langlois SF, Summers A *et al.* **Pregnancy Outcomes After Assisted Reproductive Technology.** *Journal of Obstetrics and Gynaecology Canada* 2006, **28**(3):220-233.
7. Ensing S, Abu-Hanna A, Roseboom TJ, Repping S, van der Veen F, Mol BW, Ravelli AC: **Risk of poor neonatal outcome at term after medically assisted reproduction: a propensity score-matched study.** *Fertility and sterility* 2015, **104**(2):384-390.e381.
8. Lee SH, Lee MY, Chiang TL, Lee MS, Lee MC: **Child growth from birth to 18 months old born after assisted reproductive technology—results of a national birth cohort study.** *International journal of nursing studies* 2010, **47**(9):1159-1166.
9. Rooney KL, Domar AD: **The relationship between stress and infertility.** *Dialogues Clin Neurosci* 2018, **20**(1):41-47.
10. Killersreiter B, Grimmer I, Bühner C, Dudenhausen JW, Obladen M: **Early cessation of breast milk feeding in very low birthweight infants.** *Early Human Development* 2001, **60**(3):193-205.
11. Hammarberg K, Fisher JR, Wynter KH, Rowe HJ: **Breastfeeding after assisted conception: a prospective cohort study.** *Acta paediatrica (Oslo, Norway : 1992)* 2011, **100**(4):529-533.
12. Fisher J, Hammarberg K, Wynter K, McBain J, Gibson F, Boivin J, McMahon C: **Assisted conception, maternal age and breastfeeding: an Australian cohort study.** *Acta paediatrica (Oslo, Norway : 1992)* 2013, **102**(10):970-976.
13. Cromi A, Serati M, Candeloro I, Uccella S, Scandroglio S, Agosti M, Ghezzi F: **Assisted reproductive technology and breastfeeding outcomes: a case-control study.** *Fertility and sterility* 2015, **103**(1):89-94.
14. McMahon CA, Ungerer JA, Tennant C, Saunders D: **Psychosocial adjustment and the quality of the mother-child relationship at four months postpartum after conception by in vitro fertilization.** *Fertility and sterility* 1997, **68**(3):492-500.
15. O'Quinn C, Metcalfe A, McDonald SW, Raguz N, Tough SC: **Exclusive breastfeeding and assisted reproductive technologies: a Calgary cohort.** 2012.

16. Britton C, McCormick FM, Renfrew MJ, Wade A, King SE: **Support for breastfeeding mothers.** *The Cochrane database of systematic reviews* 2007(1):Cd001141.
17. Chen DC, Nommsen-Rivers L, Dewey KG, Lonnerdal B: **Stress during labor and delivery and early lactation performance.** *The American journal of clinical nutrition* 1998, **68**(2):335-344.
18. Lau Y, Htun TP, Lim PI, Ho-Lim S, Klainin-Yobas P: **Maternal, Infant Characteristics, Breastfeeding Techniques, and Initiation: Structural Equation Modeling Approaches.** *PLoS one* 2015, **10**(11):e0142861.
19. Liu P, Qiao L, Xu F, Zhang M, Wang Y, Binns CW: **Factors associated with breastfeeding duration: a 30-month cohort study in northwest China.** *Journal of human lactation : official journal of International Lactation Consultant Association* 2013, **29**(2):253-259.
20. McDonald SD, Pullenayegum E, Chapman B, Vera C, Giglia L, Fusch C, Foster G: **Prevalence and predictors of exclusive breastfeeding at hospital discharge.** *Obstetrics and gynecology* 2012, **119**(6):1171-1179.
21. **National breastfeeding rate in Taiwan** [<https://www.hpa.gov.tw/Pages/Detail.aspx?nodeid=506&pid=463>]
22. Saadeh R, Akre J: **Ten Steps to Successful Breastfeeding: A Summary of the Rationale and Scientific Evidence.** *Birth (Berkeley, Calif)* 1996, **23**(3):154-160.
23. Zegers-Hochschild F, Adamson GD, de Mouzon J, Ishihara O, Mansour R, Nygren K, Sullivan E, Vanderpoel S: **International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) revised glossary of ART terminology, 2009.** *Fertility and sterility* 2009, **92**(5):1520-1524.
24. Edwards KI IP: **Estimated Date of Delivery (EDD).** StatPearls [Internet]: Treasure Island (FL):StatPearls Publishing; Updated 2020 Apr 30.
25. Sunderam S, Kissin DM, Flowers L, Anderson JE, Folger SG, Jamieson DJ, Barfield WD: **Assisted reproductive technology surveillance—United States, 2009.** *Morbidity and mortality weekly report Surveillance summaries (Washington, DC : 2002)* 2012, **61**(7):1-23.
26. Textor J, Hardt J, Knuppel S: **DAGitty: a graphical tool for analyzing causal diagrams.** *Epidemiology (Cambridge, Mass)* 2011, **22**(5):745.
27. Quint JK, Minelli C: **Can't see the wood for the trees: confounders, colliders and causal inference - a clinician's approach.** *Thorax* 2019, **74**(4):321-322.
28. StataCorp L: **Stata statistical software: Release 15 (2017).** College Station, TX: StataCorp LP 2017.
29. Valeri L, Vanderweele TJ: **Mediation analysis allowing for exposure-mediator interactions and causal interpretation: theoretical assumptions and implementation with SAS and SPSS macros.** *Psychol Methods* 2013, **18**(2):137-150.
30. Jakobsen JC, Gluud C, Wetterslev J, Winkel P: **When and how should multiple imputation be used for handling missing data in randomised clinical trials – a practical guide with flowcharts.** *BMC Medical Research Methodology* 2017, **17**(1):162.
31. StataCorp L: **Stata multiple-imputation reference manual.** Accessed at 2013.
32. Waits A, Guo CY, Chien LY: **Evaluation of factors contributing to the decline in exclusive breastfeeding at 6 months postpartum: The 2011-2016 National Surveys in Taiwan.** *Birth (Berkeley, Calif)* 2018, **45**(2):184-192.
33. **Assisted Reproduction Act** [<https://law.moj.gov.tw/ENG/LawClass/LawAll.aspx?pcode=L0070024>]
34. VanderWeele TJ, Vansteelandt S: **Mediation Analysis with Multiple Mediators.** *Epidemiol Methods* 2014, **2**(1):95-115.
35. Health Promotion Administration: **2016 National Report of the Assisted Reproductive Technology Summary in Taiwan.** In.: Health Promotion Administration, Ministry of Health and Welfare; 2018.
36. Harrison W, Goodman D: **Epidemiologic Trends in Neonatal Intensive Care, 2007-2012.** *JAMA pediatrics* 2015, **169**(9):855-862.
37. Haidari ES, Lee HC, Illuzzi JL, Phibbs CS, Lin H, Xu X: **Hospital variation in admissions to neonatal intensive care units by diagnosis severity and category.** *Journal of Perinatology* 2020.
38. VanderWeele T: **Explanation in causal inference: methods for mediation and interaction:** Oxford University Press; 2015.

Figures

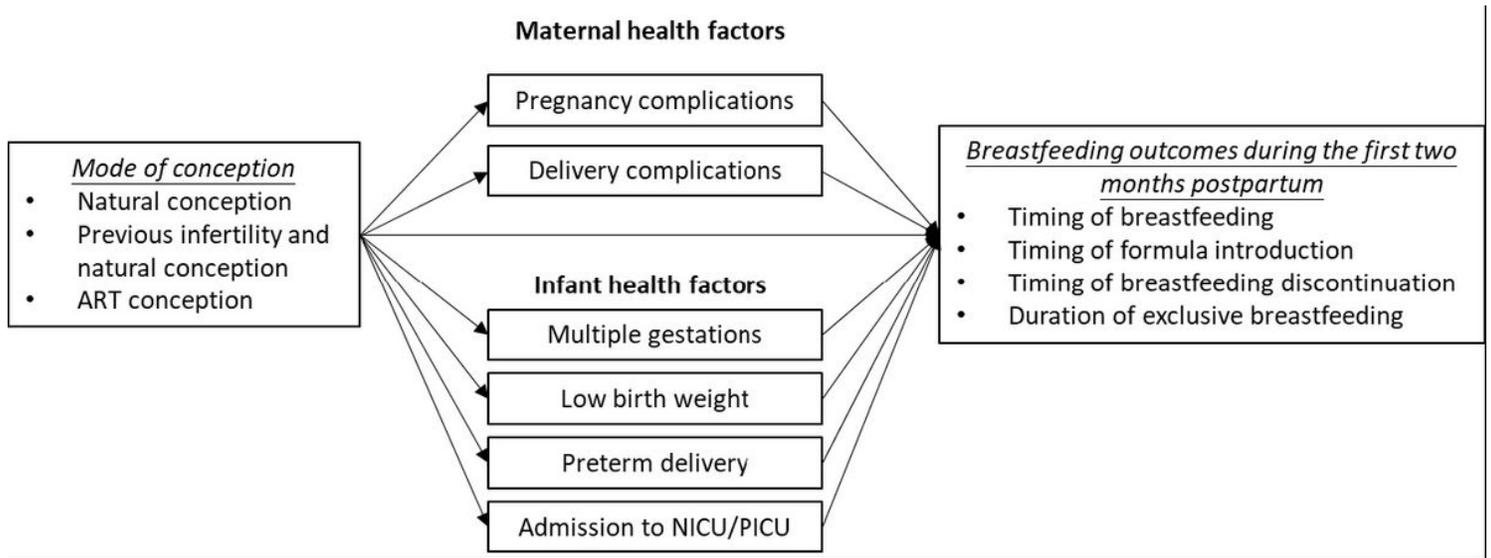


Figure 1

Hypothesised Model

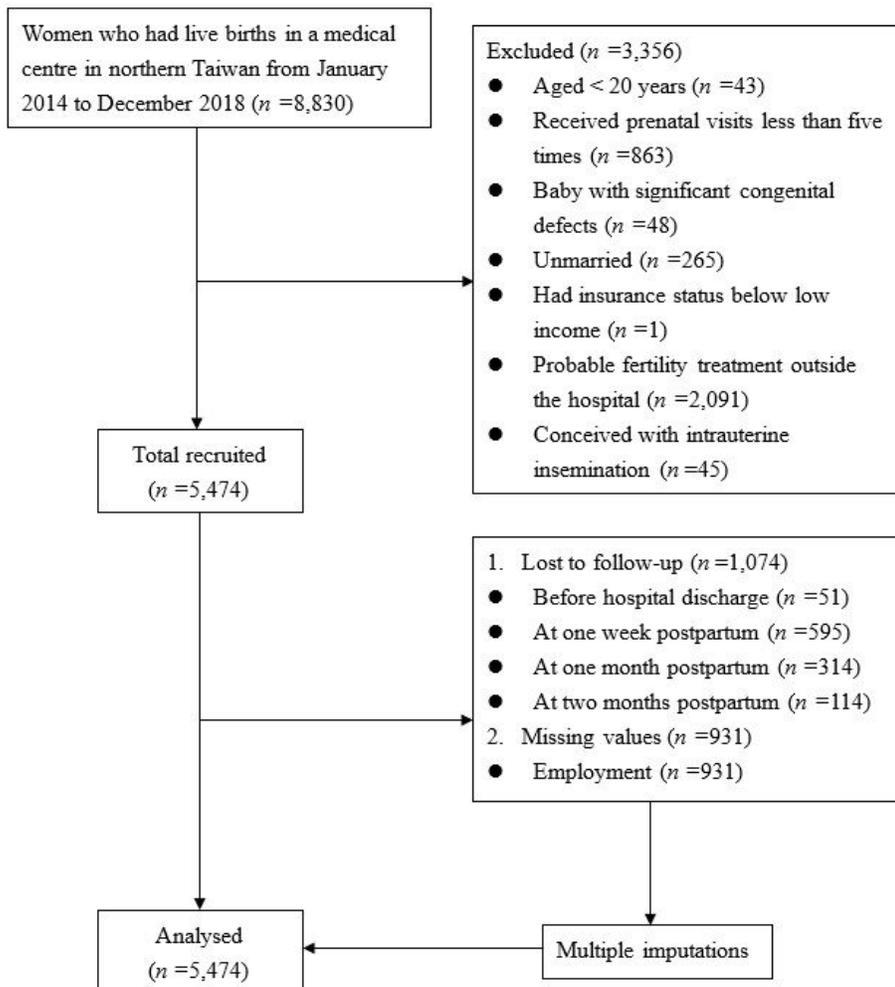


Figure 1

Flowchart of Participants.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Additionalfile1.docx](#)
- [Additionalfile2.docx](#)