To What Extent Assisted Reproductive Technology Is Risky?

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Abstract

Background: The number of infants born after assisted reproductive technology (ART) is increasing worldwide. Concerns are rising regarding its safety with inconsistent results. **Objective:** to explore maternal and child health outcomes following ART. **Method**: The current case-control study was conducted in Alexandria from January to December 2018. Target population was all children that attended El-Shatby Pediatric University Hospital during the period of study. Interviewing questionnaire, clinical examination, and radiological investigation were the tools of data collection. **Results:** The present study involved 113 singleton children born after ART and a similar number of naturally conceived controls. It showed that among ART group; subfertility was primary in 90.3% and mostly due to male factor (64.6%). The study revealed that ART mothers were more likely to have hypertension in pregnancy (OR=4.8), preeclampsia (OR= 4.3), gestational diabetes (OR=3.4) placenta previa (OR=2.8), premature rupture of membrane (OR=2.7) and Caesarean section (OR= 2.3) versus naturally conceived (NC) women. ART children were more prone to low birth weight (OR=3.2), admission to neonatal intensive care unit (OR=4.9) or hospital (OR=2.4) with longer stay (p=0.001) versus naturally conceived children. Odds of Autism spectrum disorders (OR= 5.4) and global developmental delay (OR= 4.4) were higher among children born after ART than among controls. Major and multiple congenital anomalies were more likely to be observed among ART (OR=4.5 and OR= 2.1 respectively) versus NC children. Anomalies of the cardio vascular and central nervous systems (4.4% each) were the most frequent. Adversely affected ART children (100%) were well accepted within their families and all primary subfertile mothers (90.3%) were welling to have more. **Conclusion and recommendations:** Our study confirmed an increased risk of adverse maternal and child outcome after ART. Pre-implantation genetic screening, careful neonatal examination, long term follow up of ART children, and prospective studies to assess early and delayed ART outcomes and their determinants are recommended.

Key Words: *Assisted reproductive Technology, safety, newborn*

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Introduction

Since decades, assisted reproduction technology (ART) had developed as a miracle to solve the problems of subfertile couples. Then, with the immense progress in ART, it has become a standard common procedure in obstetric practice worldwide.[1] ART is defined as "all interventions that include the in vitro handling of both human oocytes and sperm or of embryos for the purpose of reproduction."[2] This includes, in vitro fertilization (IVF); with or without intracytoplasmic sperm injection (ICSI) , gamete and embryo cryopreservation, embryo transfer (fresh or frozen/ thawed), embryo biopsy, pre-implantation genetic testing, assisted hatching, gamete and

Table (1): Characteristics of the studied children at Pediatric University Hospital, Alexandria.

Characteristic	ART[a] children N (%)	NC[b] children N (%)	Test of Significance (P)
Child Characteristics:			
Year of Birth:			
2014	14 (12.4)	14 (12.4)	
2015	13 (11.5)	13 (11.5)	
2016	15 (13.3)	15 (13.3)	
2017	31 (27.4)	31 (27.4)	
2018	40 (35.4)	40 (35.4)	
Gestational Age (weeks)**:**			
< 37 weeks	37 (32.7)	37 (32.7)	
≥ 37 weeks	76 (67.3)	76 (67.3)	
Sex:			
Male	62 (54.9)	62 (54.9)	
Female:	51 (45.1)	51 (45.1)	
Family Characteristics*:*			
Maternal Age (years**):(**Mean ± S)	33.3±4.1 (26-42)	32.8±4.4 (25-43)	t= 0.902 (0.368)
25-<35	64 (56.6)	64 56.6	
35 – 39	41 (36.3)	41 36.3	
40-43	8 (7.1)	8 7.1	
Paternal Age (years**):(**Mean ± S)	38.5±4.2 (30-48)	36.8±4.7 (27-47)	t= 2.9 (0.004) *
28-<40	69 (61.1)	75 (66.4)	χ^2= 0.69 (0.406)
40 - 48	44 (38.9)	38 (33.6)	
Parental Consanguinity:			
Yes	38 (33.6)	40 (35.4)	χ^2= 0.078 (0.780)
No	76 (66.4)	73 (64.6)	
Maternal Education:			
Illiterate/ read and write	6 (5.3)	8 (7.1)	
School Education	26 (23.0)	30 (26.5)	X_2^2= 0.80 (0.670)
University or higher Education	81 (71.7)	75 (66.4)	
Maternal Work:			
Working	27 (23.9)	31 (27.4)	χ^2=0.37 (0.542)
Not working	86 (76.1)	82 (72.6)	
Smoking Exposure in Pregnancy:			
Yes	50 (44.2)	53 (46.9)	χ^2=0.16 (0.689)
No	63 (55.8)	60 (46.9)	
Time to Pregnancy (TTP)			
≤ 1 years	5 (6.2)	105 (92.9)	χ^2=170.0 (<0.001) *
> 1 years	108 (93.8)	8 (7.1)	
Parity at time of delivery			
Primipara	87 (77.0)	87 (77.0)	
Multipara	26 (23.0)	26 (23.0)	
Antenatal Care:			
<4 visits	0 (0.0)	0 (0.0)	
≥4 visits	113 (100.0)	113 (100.0)	
Total	113 (100)	113 (100)	264 (100)

*[a] Assisted Reproduction Technology [b] Natural Conception * statistically significant*

zygote intrafallopian transfer, donation of semen, oocyte or embryo, and gestational carrier cycles. ART does not include any assisted insemination. Medically assisted reproduction is another broader term entailing the used of any procedure or medication to achieve pregnancy. In addition to ART procedures, this involves ovarian stimulation, ovulation induction, maturation triggering, uterine transplantation and any assisted insemination.[2]

The number of infants born after ART is increasing annually reaching up to 7 million

Table (2): Pregnancy Outcome by Mode of Conception.

Characteristic	Mode of Conception		OR (95% CI) P (X^2 test)
	Assisted (ART) N (%)	Natural (NC) N (%)	
Hypertension of Pregnancy (HDP)			
Yes	17 (15.0)	4 (3.5)	4.8 (1.6-14.8)
No [a]	96 (85.0)	109 (96.5)	(0.005) * [b]
Pre-/eclampsia			
Yes	12 (10.6)	3 (2.7)	4.3 -(1.2-15.8)
No [a]	101 (89.4)	110 (97.3)	(0.029) *[b]
Gestational Diabetes Mellitus			
Yes	19 (16.8)	6 (5.6)	3.4 (1.3-8.9)
No [a]	94 (83.2)	101 (94.4)	(0.009) *
Placenta Previa			
Yes	13 (11.5)	5 (4.4)	2.8(0.97-8.2)
No [a]	100 (88.5)	108 (95.6)	(0.049) *
Premature Rupture of Membrane (PROM)			
Yes	15 (13.3)	6 (5.3)	2.7 (1.0-7.3)
No [a]	98 (86.7)	107 (94.7)	(0.039) *
Caesarean Section (CS)			
Yes	99 (87.6)	77 (68.1)	2.3- (1.7-6.6)
No [a]	14 (12.4)	36 (31.9)	(<0.001) *
Antepartum Hemorrhage			
Yes	8 (7.1)	4 (3.5)	2.1 (0.61-7.1)
No [a]	105 (92.9)	109 (96.5)	(0.374) [b]
Postpartum Hemorrhage			
Yes	6 (5.3)	5 (4.4)	1.2- (0.4-4.1)
No [a]	107 (94.7)	108 (95.6)	(0.76)
Oligohydramnios			
Yes	3 (2.7)	2 (1.8)	1.5 (0.25-9.2)
No [a]	110 (97.3)	111 (98.2)	(1.0) [b]
Polyhydramnios			
Yes	4 (3.5)	3 (2.7)	1.3 (0.29-6.2)
No [a]	109 (96.5)	110 (97.3)	(1.0) [b]
Anemia in Pregnancy			
Yes	66 (58.4)	70 (62.5)	0.8 (0.5-1.4)
No [a]	47 (41.6)	42 (37.5)	(0530)
Total	113 (100)	113 (100)	

*ART= Assisted Reproduction Technology NC= Natural Conception OR = odds ratio CI = confidence interval * statistically significant [a] Reference category [b] Fisher's Exact Test*

children by 2017[3] with rising concerns regarding its safety. Some authors reported absent or minimal risk.[4-5] Different publications confirmed significant pregnancy and perinatal adverse outcomes among both mothers and offspring subjected to ART compared to natural conception (NC).[1,3,6-9] Delayed complications among ART children involved higher odds of morbidity; including non-specified and parasitic infections, genitourinary disorders, asthma, and epilepsy compared to NC children. Limited data suggested possibility of late onset cardiovascular and metabolic disorders and some childhood cancers.[3,6,10] The precise reasons for this increase in adverse outcomes are not clear. ART outcome should be assessed to ensure good health for clients.[1,6]

In Egypt, the Egyptian IVF Registry reported that 50 nationwide centers are practicing ART by 2014 with increasing number. This is added to a proportion of clinics either of small size or without records. Collected data relevant to health outcomes are incomplete.[11] Concerning researches are lacking, so the present study was designed to explore maternal and child health outcomes following ART.

Methods

A case control study was conducted in Alexandria from January to December 2018.

The target population was all children that attended to El-Shatby Pediatric University Hospital during the period of study.

Inclusion criteria were singleton children aged ≤ 5 years, born after ART. Only cases of in vitro fertilization were included, where women were asked about the steps the couple passed through before conception to ensure in vitro handling of both ovum and sperm and embryos.[2] Those who were residing in Alexandria (according to ID) with no family history of genetic disorder or pre-conception maternal illness were recruited. Inclusion criteria also included absent history of maternal exposure to X-ray radiation, infection, un-prescribed medication, or abdominal trauma during pregnancy. Exclusion criteria were twin births, non-attending mother, and cases of ovarian stimulation or assisted insemination.[2] A similar number of control children born after natural conception (NC) was selected from the same hospital at the same period. They were matched for year of birth, child sex and gestational age, parental consanguinity, maternal age at the time of conception, maternal exposure to smoking in pregnancy, antenatal care and parity at time of child birth.

Data collection: *Questionnaire:* mothers were interviewed for data collection using a pre-designed questionnaire that included socio-demographic, reproductive, and perinatal characteristics, as well health profiles of both mother and child. Women were asked several questions about each item to ensure the same answers for accuracy of data. *Examination:* involved children were clinically examined by the investigator and referred to radiological investigation if needed for diagnosis of any extra adverse outcome including congenital anomalies (CA).

Outcome measures: Outcome measures were hypertensive disorders of pregnancy (HDP), gestational diabetes, placental complications, ante/post-partum hemorrhage, oligo/poly-hydramnios, premature rupture of membrane (PROM), Caesarean section (CS), low birth weight (LBW), admission to a hospital/neonatal intensive care unit (NICU), major CA and any unfavorable outcome (either documented through reports or diagnosed by investigator).

Statistical analysis:

Data was analyzed using the ABM SPSS version 21. Frequency, mean and standard deviation, the student t-test, chi-square tests, Fisher's Exact Test, and odds ratio (OR, with 95% confidence interval, CI) were performed. Significance of the obtained results was judged at the 5% level.

Ethical considerations:

The study proposal was reviewed and approved by the Research Ethics Committee of Alexandria Faculty of Medicine. Official permissions were obtained. Benefits of the study were explained to the participating mothers and consent to participate was obtained. Collected data were kept confidential.

Results

The present study recruited 113 singleton children born after assisted reproduction technology (ART) with an equal number of matched children born after natural conception (NC) with their mother.

Table (3): Child outcome by Mode of Conception.

Characteristic	Mode of Conception		OR (CI) P (χ^2 test)
	Assisted (ART) N (%)	Natural (NC) N (%)	
Low Birth Weight:			
Yes	33 (29.2)	13 (11.5)	3.2 (1.6-6.4)
No [a]	80 (70.8)	100 (88.5)	(0.001) *
Neonatal Intensive Care Admission Unit (ICU):			
Yes	21 (18.6)	5 (4.4)	4.9 (1.8-13.6)
No [a]	92 (81.4)	108 (95.6)	(0.001) *
Hospital admission:			
Yes	21 (18.6)	10 (8.8)	2.4 (1.1-5.3)
No [a]	92 (81.4)	103 (91.2)	(0.033) *
Number of Hospital Admissions:	3.7±2.2 (1-10)	3.2±0.8 (2-4)	t=0.7 (p=0.353)
Duration of Hospital Stay: (days)	7.9±3.3 (3-14)	4.6±1.6 (3-7)	t=2.9 (p=0.001) *
Bronchial Asthma:			
Yes	19 (16.8)	17 (15.0)	1.1 (0.6-2.3)
No [a]	94 (83.2)	96 (85.0)	(0.716)
Epilepsy:			
Yes	5 (4.4)	3 (2.7)	1.7 (0.4-7.3)
No [a]	108 (95.6)	110 (97.3)	(0.472) [b]
Autism Spectrum Disorders (ASD):			
Yes	10 (8.8)	2 (1.8)	5.4 (1.2-25.2)
No [a]	103 (91.2)	111 (98.2)	(0.034) * [b]
Global Developmental Delay (GDD):			
Yes	12 (10.6)	3 2.7	4.4 (1.2-15.9)
No [a]	101 (89.4)	110 97.3	(0.029) * [b]
Attention Deficit Hyperactive Disorder (ADHD):			
Yes	9 (8.0)	4 (3.5)	2.4 (0.7-0.9)
No [a]	104 (92.0)	109 (96.5)	(0.253) [b]
Major Congenital Anomaly:			
Yes	16 (14.2)	4 (3.5)	4.5 (1.5-13.9)
No [a]	97 (85.8)	109 (96.5)	(0.008) * [b]
Types: [c]			
Multiple anomalies	6 (5.3)	0 (0.0)	0.029 * [b]
Cardio vascular system anomalies	5 (4.4)	1 (25.0)	0 .446 [b]
Central nervous system anomalies	5 (4.4)	1 (25.0)	0 .212 [b]
Genitourinary anomalies	4 (3.5)	0 (0.0)	0.122 [b]
Digestive system anomalies	4 (3.5)	1 (25.0)	0.369 [b]
Down syndrome	4 (3.5)	0 (0.0)	0.369 [b]
Head and neck	3 (2.7)	1 (25.0)	0 .247 [b]
Musculoskeletal anomalies	2 (1.8)	0 (0.0)	0 .498 [b]
Genetic disorders	2 (1.8)	0 (0.0)	1.000 [b]
Total	113 (100)	113 (100)	

*ART= Assisted Reproduction Technology NC= Natural Conception OR = odds ratio CI = confidence interval * statistically significant [a] Reference category [b] Fisher's Exact Test [c] Categories are not mutually exclusive*

Characteristics of the study population are presented in Table (1). It shows that children were matched by year of birth, where they were mostly born in the year 2018 and 2017 (35.4% and 27.4% respectively), gestational age, where 32.7%

were born before 37 weeks of gestation, and sex, where they were males dominated (54.9%). Mothers of both groups were matched by age at time of pregnancy of the studied children, where the majority were below 35 years of age (56.6%) with no significant differences between age groups or means. Although no significant differences were observed among paternal age groups at time of pregnancy, the mean age was significantly higher among ART (38.5±4.2 years) than among NC group (36.8±4.7 years). No significant differences were observed regarding parental consanguinity, maternal education and work, or exposure to smoking in pregnancy (active or passive).

Table (1) shows that parity at time of delivery and antenatal care were matched in both groups where women were mainly primipara (77%) and all (100%) received ≥4 antenatal visits. Frequency of first pregnancy after one year was significantly higher among ART compared to control mothers (93.8% versus 7.1%, p<0.001). Among ART group (data not shown); subfertility was primary in 90.3% and mostly due to male factor (64.6%). The involved ART children were born after a mean of 3.1±1.6 (1-9) preceding failed cycles and in 92.0% of instances more than one embryo was implanted. None of ART mothers reported pre-implantation genetic screening of embryo. Almost 12.4% of them had another live-birth ART sibling.

Table (2) shows that women with ART were more likely to have HDP (4.8 folds), PE (4.3 folds) and gestational diabetes (3.4 folds) compared with NC women. They also had higher probability to have placenta previa (2.8 folds), premature rupture of membrane (2.7 folds) and to deliver through CS (2.3 folds) versus NC women. Differences were insignificant among the two groups regarding ante- and postpartum hemorrhage, oligo- and polyhydramnios and anemia in pregnancy.

Table (3) reveals that newborns after ART were 3.2 times more likely to be of LBW and 4.9 times to be admitted to NICU compared to births after NC. Children of ART group were 2.4 folds more likely to be admitted to hospital versus control children and to stay longer in hospital (7.9±3.3 versus 4.6±1.6 days, p=0.001). Frequency of bronchial asthma and epilepsy did not differ significantly between both groups. Odds of autism spectrum disorders (ASD; OR= 5.4) and global developmental delay (GDD; OR= 4.4) was more likely to be higher among children born after ART than NC children. No significant group differences were observed among attention deficit hyperactive disorder (ADHD). Major congenital anomalies were 4.5 times more likely to be observed among ART versus NC children. Anomalies of the cardio vascular and central nervous systems (4.4% each) were the most frequent followed by that of genitourinary and digestive system and Down syndrome (3.5% each). Multiple anomalies were only encountered among ART children (5.3%) who were 2.1 folds more likely to be affected compared with NC. Adversely affected ART children (100%) were well accepted within their family and all primary subfertile mothers (90.3%) were welling to have more. (data not shown)

Discussion

After widespread use of ART, despite great benefits, worries have pushed many researches to investigate its safety among both mothers and offspring. Results of these studies were inconsistent. Some authors[4-5] observed no differences in obstetric complications between ART and NC, except for first trimester vaginal bleeding in women with polycystic ovary.[4] In contradiction, studies from different countries including Egypt recorded higher risk of pregnancy complications among ART versus NC. Preterm delivery, CS,

placenta complications, gestational diabetes, HDP, PE, uterine bleeding, polyhydramnios, and anemia were more prevalent in ART than in NC mother.[1,6-9,12,13] Ovarian hyperstimulation syndrome and bleeding / infection following oocyte retrieval were also reported in the Egyptian national report of ART, 2014.[11]

The present study recorded consistent results. It observed increased risk of CS among ART (87.6%) versus NC group (68.1%). Other studies were in agreement, with reported near figures in Egypt[12] an Saudi Arabia[13] and much lower values in United States[7] and Australia.[8] In harmony with prior authors,[7,9] our study reported significantly higher odds of gestation diabetes, HDP, PE and placenta previa in ART compared with NC. In contrast, Abdel-Baset et al[5] observed no extra risk of PE or placenta complications in ART. Further, premature rupture of membrane was significantly associated with ART versus NC. This is consistent with earlier findings in Egypt[12] and China[9], and contradicting that of Qatar.[5] While prior studies observed significant association between uterine bleeding and ART[4,7,8], the current, similar to Abdel-Baset et al[5] failed. Davies et al[8] observed significantly higher frequency of anemia among ART versus NC which was not the case in our results.

Compared to NC, Farhi et al[4] reported absent significant perinatal risk among infants born following ART, apart from prematurity and low birth weight (LBW) that associated IVF. To the contrary, several studies, including Egyptian ones, documented increased risk of prematurity, small for date, LBW, low Apgar scores, CA, and perinatal and infant death among ART births.[1,3,6-9,11,12] Our results revealed increasing risk for LBW among ART versus NC births while premature constituted about one third [32.7%, table (1)] of cases and controls. General agreement regarding the increased risk of prematurity and LBW among ART was seen in previous Egyptian[11.12] and non-Egyptian studies.[1,3,4,6-9, 13] Mansour et al[11] recorded consistent national premature rate (25%-36%) among ART in Egypt. This study also observed higher odds of both major (OR=4.5) and multiple (OR=2.1) CA in ART than in NC children. Prior results were inconsistent. In the same age group, Davies et al[8] confirmed similar increased risk among major and multiple CA. Among infants, while numerous studies observed higher risk of CA in ART compared to NC[1,6-8,14], others failed.[4,5,13]

In Egypt, Mansour et al could not estimate the frequency of CA due to incomplete reporting. In Cairo, Bassiouny et al[12] reported higher incidence of CA among ICSI (2.31%) compared to NC births (1.86%), while Aboulghar et al[15] reported the reverse (1.3% versus 1.9%). Although differences were insignificant in both studies, discrepancy may be explained by the fact that Bassiouny et al conducted postnatal examination of the ultrasound-detected (antenatal) case while Aboulghar et al did not.

The frequency of CA in our study (14.2%) is much higher than the previously recoded figures in ART infants both in Egypt and other countries which ranged between 2.1%-8.4%.[4-8,12-14] It is also higher than Davies' et al rate in the same age group (8.3%).[8]

In the current study, cardio vascular (4.4%) and central nervous (4.4%) system anomalies were the most frequently observed CA followed by genitourinary (3.5%) and digestive system anomalies (3.5%). The rates and orders of the involved systems varied in the previous reports. Prior studies observed the highest proportion among cardio vascular (2.8%)[5], urogenital (3.5%)[14], musculoskeletal (3.0%)[8], and cleft palate (1.19%) anomalies.[13]

The studied ART children were more likely to be admitted to NICU, to be hospitalized

and to stay longer in hospital than NC children. Abdel-Baset et al[5], recorded consistent higher odds of NICU admission and Kettner et al[10] reported consistent risk of hospital admissions and length of hospital stay.

Our analysis of data revealed higher odds of autism spectrum disorders among ART children compared to NC controls. Previous findings were inconclusive. Liu et al reported a similar significant association.[16] While Lehti et al[17] observed insignificant association, he described higher risk among ART singletons versus multiples and among ART boys versus girls.

Study results showed increased risk of global developmental delay among children born after ART versus controls. At 2 years of age, earlier studies recorded comparable risk among ART versus NC group and among different ART techniques and types.[18,19] On the other hand, Punamaki et al[19] observed significantly higher levels of cognitive problems in ART girls compared to NC girls whereas the reverse was observed among boys.

The adverse outcomes of ART conceptions are multifactorial, and it is not clear to what extent ART procedures, parental characteristics and genetic elements contribute to this outcome.[1,3,6,10] ART procedures may have an effect involving hormonal therapy, surgical retrieval of oocyte, external handling of gametes or embryo, ICSI, culture in external media, biopsy, freezing/thawing, and transfer.[1,3,6,9,20] Some may be associated with impaired placental and fetal growth and development, altered epigenetic regulations and a consequent affected fetus and child. Also, components of culture media may affect growth patterns and birth-weights, while culture to the fifth day may be associated with preterm labour.[3,6]

Freezing/thawing in ART may damage cell membranes and disturb internal cellular media, organelles and function. It may also affect DNA integrity.[21] The Egyptian IVF Registry, 2014[11] and a meta- analysis[20] reported supporting findings included increased risk/ frequency of obstetric and perinatal complications as well perinatal mortality among frozen versus fresh embryo transfer. On the other hand, some studies observed lower risk of perinatal complications and comparable risk of CA and perinatal mortality among frozen versus fresh embryo.[8,20,22]

Adding to the proposed damaging effect the invasive ICSI, it is used to treat subfertile males who may already have damaged sperm DNA. These may cause congenital or chromosomal anomalies. Also, bypassing the natural selection of sperm may enable sperms of low criteria to overcome the egg barrier resulting in unfavorable outcome.[1,3,6,23] Davies et al[8] confirmed higher risk of CA among ICSI compared to IVF, whereas Egyptian[12] and Middle East studies revealed no risk versus NC.[12,13] Further, while some Egyptian and non-Egyptian authors[13] reported increased risk of obstetric complications and neonatal deaths versus NC, Zhu et al[9] observed no extra risk versus IVF. Limited data suggests impact on male, but not female, fertility among offspring conceived via ICSI.[3]

Regarding non-ART factors, paternal characteristics and health profile were described.[1,3,6] However, with our study inclusion criteria and after matching of main characteristics, still there was a risk. Multiple pregnancies, due to multiple embryo transfer, is considered the most powerful predictive factor for adverse outcomes.[1,6,13] Twinning may be related to higher risk of preterm labour and LBW which, in turn, can adversely affect postnatal as well delayed health outcomes. Other obstetric and perinatal complications were seen in previous reports.[1,6,9,13] Different authors disagreed and observed comparable risk of obstetric and perinatal complications among ART twins compared

to NC twins.[5,9] Davies et al[8] also observed comparable risk of CA among multiples versus singletons, even with less systems involved in CA. On the other hand, singleton pregnancies were significantly associated with adverse maternal and child outcomes versus NC in the present and previous works.[1,6,8,9,14] Davies et al[8] explained this contradiction by the fact that a high proportion of singleton pregnancies after ART may result from vanishing twins or triplets which are responsible for the adverse effects. In support, most of our singletons were born after implantation of more than one embryo.

Underlining causes of subfertility that indicate ART as well as infertility treatment may also play a role in the reported adverse outcomes.[1,3,6] A number of large population studies observed increasing maternal and infant adverse outcomes among both subfertile and ART groups versus NC group and linked these outcomes to subfertility itself with or without ART.[7,8,24] On the other hand, Declercq et al[24] revealed that the risk was higher among subfertile ART versus subfertile NC groups. This denotes that ART contributes to the etiology. Luke's et al[7] explains that subfertility among ART may be more severe with more extensive underlying pathology or other harmful factors. Impact of female subfertility could not be examined in our analysis due to the small number of subfertile NC women. On the other hand, our frequency of male factor subfertility (64.6%) was higher than the previously observed rates[4,13] and might contribute to our findings.

Heterogeneity in the outcomes may be attributed to the difference in the number, age and parental background of study population, different methodology, adopted definitions/classifications and quality of reporting/recording system. Besides, variability in ART procedures, quality of the provided health services may also affect outcome. In addition, ART children, with over caring parents, may be over presented in health services. Also, some proportion may not be presented due to early loss or good health.

Conclusion

Our study confirmed an increased risk of adverse maternal and child outcome after ART compared to spontaneous conceptions.

Recommendations

Our study recommends the following: Pre-implantation genetic screening. Counseling couples about the possibility of associating risks prior to ART. Close obstetric surveillance of ATR conceptions with ultrasound screening for CA. Careful postnatal assessment of neonates. Long-term follow-up of ART children. Further large scale, well-controlled prospective studies to assess early and delayed ART health outcomes and their determinants. Screening of ART outcomes in the national health demographic survey. Further studies to examine magnitude of male fertility and associated factors.

Strengths and Limitations

Screening a topic of limited data in Egypt and obtaining health profile of children up to 5 years with the presence of normal control constitute study strength. Some of the study limitations are the very small number and absence of subfertile controls. Being a case control study limited exploration of some variables which may be confounders or outcomes. Also, results cannot be generalized.

Acknowledgements

The authors acknowledge all the participants. We are very grateful to Ahmad M. Gomaa MB ChB, Faculty of Medicine, Alexandria University, Egypt for helping in data collection. Sincere gratitude goes to Prof. Asmaa Abdu El-Aziz, Community medicine Department, Faculty of Medicine, Alexandria University, Alexandria, Egypt

for revising the manuscript and for her valuable comments.

Conflicts of interests

The authors declare no competing interests.

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