



Outcome and Congenital Anomalies in Children Born after Assisted Reproductive Technology in Port Harcourt

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Authors' contributions

This work was carried out in collaboration between all authors. All authors contributed to the study concept and design. Author NO designed, wrote the protocol and wrote first draft of the manuscript.

Author PF performed the statistical analysis. Authors PT and BO carried out the interview and physical examination/echocardiogram of the patients. Authors NO and RA managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aim: To evaluate the outcome of children born following Assisted Reproductive Technology in Port Harcourt, Nigeria.

Study Design: A retrospective study.

Place of Study: Department of Paediatrics, University of Port Harcourt Teaching Hospital, Port Harcourt.

Methods: Fifty ART-conceived-children (subjects) and 50 spontaneously conceived children (controls) between 2004 and 2013 were studied. The subjects were recruited from the treatment records of The Bridge Clinic, Port Harcourt. Those who gave consent were invited to the paediatric

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clinic of the University of Port Harcourt Teaching Hospital (UPTH) between January 2014 and June 2014 where they were interviewed with a structured questionnaire. Data collected was collated and analysed with Epi Info Ver. 6.04d.

Results: The mean gestational age at delivery (36.3 ± 3.1 versus 38.9 ± 1.2 weeks) and the mean birth weight (2.6 ± 0.8 versus 3.4 ± 0.5 kg) were significantly lower in the cases than controls. There was a higher incidence of congenital anomalies in the ART babies 17(34%) versus 0(0%) [OR 25.24, 95% CI: 3.25 - 53.19]. Admission into the Neonatal Intensive Care Unit (NICU) was also significantly higher in the ART babies, 15(30%) versus 3(6%) [OR 6.53, 95% CI: 6.23 - 30.90].

Conclusion: The children born from ART in Port Harcourt had more adverse outcome than spontaneously conceived children with respect to preterm birth, lower birth weight, neonatal admission and congenital anomalies. Patients should be adequately counseled on these outcomes before they embark on assisted conception.

Keywords: Assisted reproductive technology; outcome; congenital anomalies; Port Harcourt.

1. INTRODUCTION

The prevalence of infertility is increasing globally more so in Nigeria and many parts of Sub-Saharan Africa [1,2]. Assisted reproductive technology (ART) has been used widely for treatment of infertile couples when conventional treatments are unsuccessful. There is growing concern, however about the health of children born after this form of treatment. Interventions used in ART such as hormonal stimulation, oocyte retrieval, *in vitro* fertilisation (IVF), intracytoplasmic sperm injection (ICSI), embryo culture and intra uterine embryo transfers may contribute to health risks in children born following ART. Questions arise with regards to its safety especially with ICSI, which is thought to circumvent the natural selection process of fertilization of sperm and ova [3].

Published data on children born following ART reveal more adverse neonatal outcomes and increased congenital anomalies than in the general population. There are reports of higher prevalence of heart malformations in the IVF population than in the general population [4-8].

Treatment by ART results in multiple pregnancies, which are associated with increased risks of pre term delivery, low birth weight, congenital anomalies and perinatal deaths. However, singleton IVF pregnancy is associated with increased risk of low birth weights, preterm births and congenital malformations compared with spontaneously conceived singletons [9,10,11].

Assisted Reproductive Technology is associated with a 30% to 40% increased relative risk of major congenital anomalies compared with natural conceptions [10,11]. These anomalies include septal heart defects, cleft lip, oesophageal atresia, anorectal atresia and

hypospadias [12,13,14]. Historically, the Lancaster study was the first to report a greater than expected incidence of babies with neural tube defects and transposition of great arteries following ART [15]. Thereafter, studies from Sweden, Australia, France and Germany have shown similar results [16-20].

Infertility may be genetic in origin and ART treatment may facilitate intergenerational transmission. Children born following ART may express a greater number of genetic abnormalities such as cystic fibrosis, microdeletions of long arm of the Y-chromosomes and imprinting syndromes. Out of nine imprinting syndromes, three are linked with ART: Beckwith – Wiedeman syndrome (BWS), Angelman syndrome (AS), and maternal hypomethylation syndrome [21].

There is paucity of data on the outcome of children conceived by ART in Nigeria. The aim of this study was therefore to evaluate the outcome of children born following ART in Port Harcourt.

2. MATERIALS AND METHODS

2.1 Study Area and Population

This was a case-control study involving 50 children conceived by ART (subjects) and 50 spontaneously conceived (controls) children. The subjects were recruited from The Bridge Clinic, Port Harcourt where ART was carried out before conception. The Bridge clinic was established in 2004 as the first ART centre in Southern Nigeria. Women who had successful treatment and singleton delivery between 2004 and 2013 were identified from the clinic's records and contacted by telephone. There were 1040 Intracytoplasmic sperm injection (ICSI) treatment cycles done for 814 women at the Bridge clinic during the period

under review. Within the period, 223 live births occurred of which 149 were singletons. Of the 149, 50 (34%) consented to the study. Nine subjects out of the 149 had relocated to other cities in Nigeria and 12 could not be reached with the contact telephone number provided so were excluded. Those who gave consent were then invited to the paediatric clinic at the University of Port Harcourt Teaching Hospital (UPTH) between January 2014 and June 2014 where they were interviewed with a structured questionnaire. The paediatrician also examined the children and an echocardiogram was carried out for those with suspected cardiac defects. The controls were 50 spontaneously conceived children who attended the paediatric clinic during the study period. The next attendee matched for age and sex to the subject was randomly selected for the study. The main outcome measures were duration of pregnancy, birth weight, perinatal morbidity and congenital malformations.

The Ethics Committee of the University of Port Harcourt Teaching hospital gave approval for the study.

2.2 Statistical Analysis

Information collected from the structured questionnaire was entered into Epi Info Ver.

6.04d, which was used for data analysis. Association between ART treatment and selected neonatal variables were assessed using the chi-square and the two-tailed Fisher exact test. Differences were considered statistically significant when $p \leq 0.05$. The results are presented as mean with standard deviations, percentages, odds ratio, rates and proportions.

3. RESULTS

There were statistically significant differences in the mean age and gestational age of mothers of the subjects compared to the controls. The mean birth weight of ART children were significantly less than spontaneously conceived children while incidence of low birth weight (LBW), congenital malformations and admission into Neonatal intensive care unit (NICU) were significantly higher among the ART children (Table 1).

Table 2 shows the maternal complications during pregnancy. It was observed that obstetric complications were significantly higher in the ART mothers with hypertensive disorders being the most common complication encountered.

The caesarean section rate was significantly higher in ART births as shown in Fig. 1.

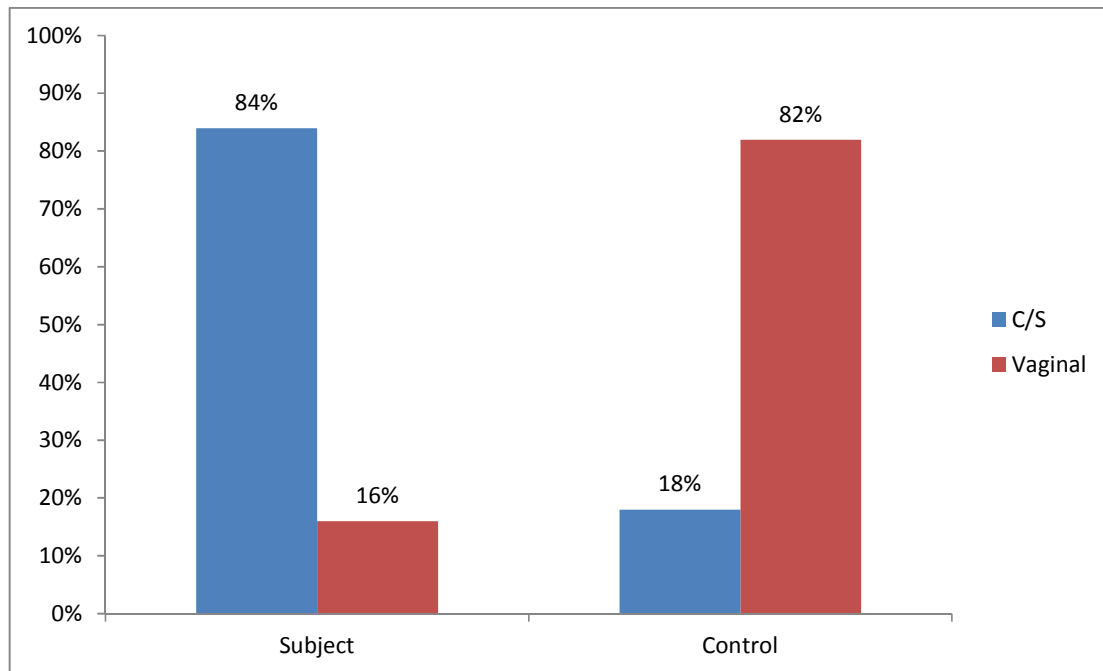


Fig. 1. Mode of delivery

Table 1. Maternal and neonatal characteristics

Variable	Subject n=50		Control n=50		Student t- test	Chi-square (χ ²)	p-value	OR (95% CI)
	Mean±SD	Freq (%)	Mean±SD	Freq (%)				
Maternal age	33.25±5.22		38.14±5.12		4.74		0.001*	
GA delivered	36.27±3.05		38.87±1.15		5.64		0.001*	
Pre-term delivery (<37 weeks)		20 (40)		1 (2)		12.77	0.001*	20.0 (2.66-05.09)
Sex								
Male		27 (54)		21 (42)		0.29	0.591	
Female		23 (46)		29 (58)		0.25	0.614	
M:F ratio		1.2:1		0.7:1				
Mean BW	2.6±0.78		3.4±0.5		5.99		0.001*	
LBW < 2.5 kg		22 (44)		4 (8)		16.84	0.001*	
Congenital Malformation		17 (34)		0 (0)		10.53	0.001*	25.24 (3.25-53.19)
Neonatal admission in NICU		15 (30)		3 (6)		5.57	0.001*	6.53 (6.23-30.90)

*Statistically Significant (p<0.05); # Fisher exact; OR=Odds Ratio; 95%CI= Confidence Interval

Table 2. Maternal complications during pregnancy

Complication	Subject (n=50) n (%)	Control (n=50) n (%)	Chi-square (χ ²)	p-value	OR	95% CI
Hypertensive disorders	16 (32)	3 (6)		0.026*		
PROM	4 (8)	0 (0)		0.07 [#]		
OHSS	1 (2)	0 (0)		0.505 [#]		
Urethral prolapse	1 (2)	0 (0)		0.505 [#]		
Fibroid degeneration	0 (0)	1 (2)		0.505 [#]		
Total	22 (44)	4(8)	8.73	0.001*	8.84	2.51-34.08

*Statistically Significant (p<0.05) # Fisher exact

PROM: Premature rupture of membranes; OHSS: Ovarian Hyper stimulation syndrome

Table 3. Correlation between maternal age and congenital anomalies in the subjects

Maternal age	Congenital anomalies		Total	Chi-square (χ ²) (p-value)
	Yes (%)	No (%)		
≤ 35	5 (29)	7 (21)	12 (24)	0.086 (0.769)*
≥36	12 (71)	26 (79)	38 (76)	
Total	17	33	50	

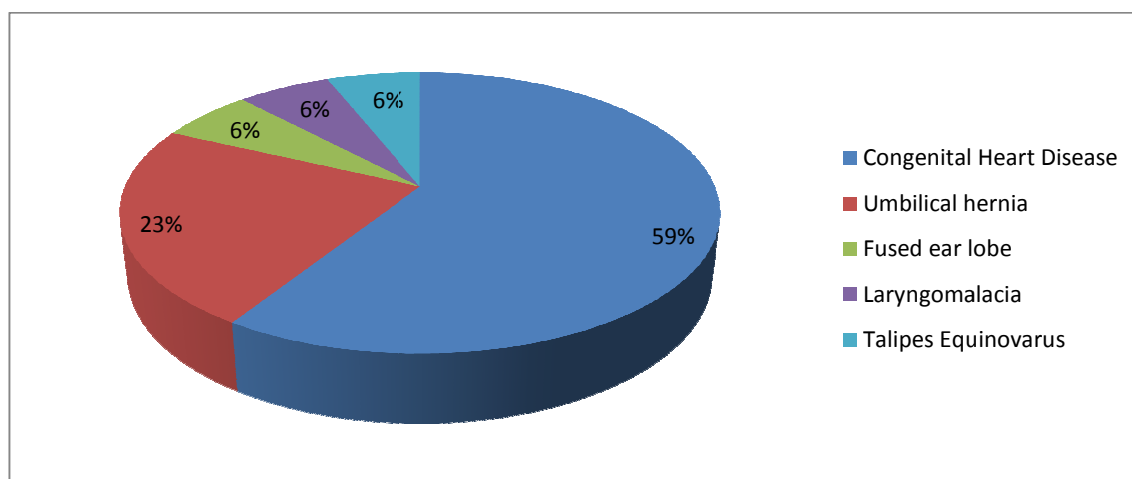


Fig. 2. Pattern of congenital anomalies

Fig. 2 showed the pattern of congenital anomalies encountered among the children born. Congenital heart anomalies accounted for 10(59%) of all the anomalies. Of these, there was 1 solitary atrial septal defect (ASD), 1 solitary ventricular septal defect (VSD), 5 combined atrial septal defect (ASD) and patent ductus arteriosus (PDA), 2 combined ASD and VSD, 1 solitary tetralogy of Fallot (TOF).

Further analysis correlating maternal age with incidence of congenital anomalies, as shown in Table 3, revealed no significant relationship between the higher incidence of congenital anomalies in mothers 36 years and above compared to those 35 years or less.

The incidence of prematurity was significantly higher in the subjects than the controls admitted into the NICU.

Table 4. Indications for admission into NICU

	Subject n (%)	Control n (%)	p-value
Jaundice	4 (8)	1 (2)	0.359 [#]
Anaemia	3 (6)	0 (0)	0.241 [#]
Prematurity	8 (16)	1 (2)	0.04*
Respiratory distress	0 (0)	1 (2)	0.505 [#]

*Statistically significant (p<0.05); # Fisher exact

4. DISCUSSION

The use of assisted conception in Nigeria has increased since the beginning of its practice following the pioneering work of Professor Osato Giwa-Osagie at the Lagos University Teaching Hospital, Lagos [22]. However, there is a paucity of data on births from ART in Nigeria, as we do not have a National birth registry. This study is the first to evaluate the neonatal outcomes and congenital malformations in children born after ART in Port Harcourt, Nigeria.

The mean gestational age of 36.3 ± 3.1 weeks among the ART group was significantly lower than that of the control in this study as against that of Koivurova et al. where there was no difference between both groups [4]. Koivurova et al study however was population based.

The mean birth weight in this study was significantly lower and the incidence of LBW significantly higher in the ART babies than that of the control group as seen in other studies [4,9,23]. This could be explained by the fact the gestational age at delivery was lower, thus a pointer that prematurity caused the LBW as established by previous report [23]. However, other factors such as the characteristics of the mother or father may also influence the risk of LBW and cannot be ruled out [23].

We found an increased prevalence of congenital anomalies especially of cardiac defects among ART conceived babies as reported in previous published data [4,7,12,13,15,24]. The numbers detected (17-34%) seem quite high compared to the 1.9% detected by Ezechi et al. [25]. We attribute this to the fact that probably mothers who consented to the study already had concerns about their babies and the babies were followed up for a longer period. Intracytoplasmic sperm injection was the ART method the women had. Intracytoplasmic sperm injection is considered more risky than conventional IVF as it is more invasive although it has higher fertilization rate. Pregnancies conceived by ICSI may be at increased risk of chromosomal aberrations including sex chromosomal anomalies [26]. We did not record any case of chromosomal anomalies or neural tube defect; this may be because the overall number of babies studied was quite few compared to other reports.

Many factors have been suggested to explain the higher incidence of congenital anomalies in ART conceived children but parental subfertility has been highlighted as the most likely cause due to reports of studies showing higher frequency of birth defects in couples that conceived spontaneously [27,28,29]. It may become necessary to genetically analyze all products of conception following ART as this may be the only way to establish malformation rate if we consider the fact that congenital anomalies incompatible with life may have resulted in early pregnancy loss [25].

This study did not show any significant relationship between the higher incidence of congenital malformation detected in the babies born to older mothers (> 35 years) of the ART group even though from the literature it is well known that ART children are at increased risk of congenital malformations even after adjustment for known confounders such as maternal age [30].

In the Koivurova et al. study, neonatal morbidity including all the most common complication was over twice as high in the babies born via assisted conception than the naturally conceived ones. Consequently, they required admission to the NICU three times more than the control [4]. Similarly in this study, babies born via ART required greater admission into the NICU with prematurity being the commonest indication.

In this study, obstetric complications were higher in the ART mothers (44%) than in the non-ART mothers (8.0%). The complications included hypertensive disorders of which its incidence in the subjects was significantly higher than in the controls. This has been suggested by previous reports [25,31]. This may account for the higher incidence of prematurity and low birth weight, as these complications usually require emergency delivery.

The relatively small number, retrospective nature and the fact that it is hospital based limit this study. Also, we did not control for other confounding factors such as body mass index. A population-based study with a larger sample size is needed to further confirm these findings in our environment. Until then, infertile couples should be counseled prior to any ART procedure about the risks associated especially that of congenital structural anomalies. Routine anatomic ultrasound for congenital structural abnormalities is recommended for ART pregnancies and a

need for closer surveillance for children conceived via such pregnancies in Nigeria exists. However, the social stigma attached to these children in Nigeria may make this surveillance somewhat difficult.

5. CONCLUSION

Children born following assisted conception had more adverse outcomes when compared to their naturally conceived counterparts in terms of preterm birth, low birth weight, admission into NICU and an excess of congenital anomalies especially cardiac defects. This information will be useful in counseling couples that intend to conceive by ART. We recommend that children born by ART in Nigeria be screened for congenital anomalies especially congenital heart disease.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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