British Journal of Medicine & Medical Research
19(7): 1-9, 2017; Article no.BJMMR.30044
ISSN: 2231-0614, NLM ID: 101570965

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Maternal and Fetal Outcome after Assisted Conception in Port Harcourt, Nigeria

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Authors' contributions

This work was carried out in collaboration between both authors. Author NO did the study design and wrote the protocol. Author JA did the statistical analysis and literature searches. Both authors did the study analyses, read and approved the final manuscript.

Article Information

DOI: 10.9734/BJMMR/2017/30044
Editor(s):
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Complete Peer review History: http://www.sciencedomain.org/review-history/17678

Original Research Article

Received 14th October 2016
Accepted 26th January 2017
Published 30th January 2017

ABSTRACT

Background: The introduction of assisted reproductive technology (ART) has played a major role in reducing the burden of infertility among couples. Although most pregnancies following assisted conception will progress normally without any increased risk to the mother or baby, studies have shown that some women who conceive in this manner as well as their babies are indeed at increased risk of complications.
Objective: To evaluate the maternal and neonatal outcome after assisted reproductive technique (ART) in Port Harcourt, Nigeria.
Materials and Methods: A retrospective case control study of 51 women who conceived via ART (subjects) and 51 women who conceived spontaneously (control) managed at the obstetric unit of the University of Port Harcourt Teaching Hospital, (UPTH), Nigeria over an 8-year period was conducted. Data obtained from theatre records and case notes of patients were analysed using the statistical package SPSS 20.
Results: The rate of multiple pregnancy was 47% (24 women) in the ART group compared with

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6% (3 women) in the control group and this was statistically significant (p = 0.001). Thirty-one (61%) of the women had adverse outcomes in the ART group compared to 9 (18%) in the control group and this was statistically significant (p = 0.001). Early pregnancy bleeding (p =0.03), hypertensive disorders of pregnancy (p = 0.05), pre term delivery (p = 0.002) caesarean delivery (p = 0.001), low birth weight (p = 0.001) neonatal admission (p = 0.02) and perinatal deaths (p = 0.03) were significantly commoner in the assisted conception group. The rates of antepartum haemorrhage, diabetes mellitus, postpartum haemorrhage, maternal death and mild birth asphyxia were not statistically different between the two groups.

Conclusion: ART pregnancies are associated with more adverse feto-maternal outcomes compared with spontaneously conceived pregnancies.

Keywords: Assisted reproduction; maternal outcome; neonatal outcome; pregnancy complications; Port Harcourt.

1. INTRODUCTION

Infertility is common worldwide with prevalence estimates of more than 186 million ever-married women of reproductive age group maintaining a "child-wish" and with high global levels of infertility that have hardly changed between 1990 and 2010 [1,2]. The scenario in Africa is different as the culture places a high premium on conception and childbirth such that infertile couples are often stigmatized and discriminated against making infertility a major public health and social problem [3]. In less resource countries like Nigeria, infertile women seek expert care late because they would have sought unorthodox treatment at homes of traditional caregivers, spiritualists and churches, making their cases more complicated [4].

Limitations of conventional treatment options for infertility have been well documented leading to the evolvement of Assisted Reproductive Techniques (ART). Despite the initial reservations about practise of ART coupled with the perceived reasons for its projected failure in Africa, [4,5] assisted conception has brought hope to millions of infertile couple in Nigeria. Although we lack accurate statistics regarding the number of ART cycles done in Nigeria due to the absence of a national registry, there are currently 43 *in vitro* fertilization (IVF) centres with 35 being privately owned and more on their way to being established, following the pioneering work of Professor Osato Giwa-Osagie at the Lagos University Teaching Hospital, Lagos [3,6]. In Southern Nigeria, the first ART centre was established in 2004 in Port Harcourt by the Bridge Clinic and to date there are 8 ART centres all privately owned. Thus ARTs have become accepted as an alternative to natural conception, and pregnancies resulting from them being increasingly managed in obstetrical departments. Infertile women form the majority of cases seen in our gynaecology clinic at the University of Port Harcourt Teaching Hospital (UPTH) and for most that require ART, the cost is out of reach. Thus, mainly the rich and growing middle class populations that can afford the cost of treatment, access ART in Nigeria. This is also what obtains in most resource-poor countries.

The success rates of IVF are assessed through achievement of pregnancy and live birth but questions arise with regards to its safety as it involves several steps that include hormonal stimulation, oocyte retrieval, fertilization, embryo culture and intra uterine embryo transfers. These steps can cause health risks in the long and short run [7]. Although most pregnancies after assisted conception result in healthy outcomes, an increased risk for a number of obstetric and neonatal complications such as preeclampsia, early pregnancy bleeding, placenta praevia, caesarean delivery, preterm delivery, lower average birth weight, and congenital malformations, compared to naturally conceived pregnancies, has been reported among singletons and twins [8-16]. This fact can be explained partly by the high rate of multiple pregnancies as a result of these procedures, and by advanced maternal age [17]. Previous studies have specifically addressed perinatal outcomes following assisted conception compared with spontaneous conception after controlling for maternal age, parity, multiple gestations, and other factors. Most studies found increases in preterm birth, low birth weight (LBW), or small for gestational age (SGA) while others did not [18-22]. A recent study done in Japan demonstrated that maternal factors associated with infertility rather than ART procedures, might contribute to the adverse outcomes [23].

Considering the paucity of information on the frequency of assisted reproductive techniques, obstetric and neonatal outcome after assisted

conception despite the increase in its use in Nigeria, this study sought to evaluate the maternal and neonatal outcomes of pregnancies following assisted conception managed at the UPTH, Port Harcourt, Nigeria. This study will also serve as a preliminary evaluation of ART pregnancies managed at the UPTH prior to the start of its own assisted conception unit.

2. MATERIALS AND METHODS

2.1 Study Area and Population

This was a retrospective case control study of all pregnant women who had conceived via assisted conception and were referred to the University of Port Harcourt Teaching Hospital (UPTH) between January 1, 2008 and December 31, 2015 for management. This study was carried out at the obstetric unit of the UPTH, which is a tertiary hospital with an average of 2,800 deliveries conducted annually. It has the highest delivery rate among all the health facilities in Rivers State. Its focus is on service delivery to our target population, research, medical education and training of students, resident doctors, nurses and other health professionals. The hospital has approximately 890 bed spaces with the obstetric unit having a total of 135 beds. There are 30 beds in the antenatal ward, 40 beds in the postnatal ward, 40 beds in the unbooked lying in ward, 17 beds in the labour ward and 8 beds in private/semi-private rooms. There are five units; each unit has four consultant obstetricians, five specialist senior registrars and two registrars with many experienced nurses and midwives. The obstetric unit caters for both groups of patients that registered for antenatal care and those that come in as obstetric emergencies. The Ethics Committee of the University of Port-Harcourt Teaching Hospital gave approval for the study.

The women were referred from the private clinics that practise assisted conception in and around Port Harcourt environs. In Southern Nigeria, the first ART centre was established in 2004 in Port Harcourt by the Bridge Clinic and to date there are 8 ART centres all privately owned. The subjects' pregnancies were confirmed by quantitative beta hCG and transvaginal ultrasound scan and were usually indicated in the case notes as "IVF pregnancies". The controls were derived from the labour ward register as the next delivery from a spontaneously achieved conception matched by maternal age.

Only women who delivered after the gestational age of foetal viability taken as 28 weeks in our environment and seen up to six weeks of the puerperium were included in the study. The theatre records, delivery registers and case notes of these women over the period under review served as the source of data from where the variables analysed were retrieved. These outcome variables included maternal parameters: i.e. socio-demographic features, indication for and type of assisted conception, number of attempts, number of embryos transferred (among the ART group), pregnancy complications, mode of delivery and maternal mortality. Foetal parameters included gestational age, number of babies, birth weight, APGAR score, indication for special care baby unit (SCBU) admission and death of the infant. The cost of the procedure was also considered. The proforma for each patient was checked for completion before it was entered into a spread sheet and analysed. However, all the information needed was not gotten, as there were some missing values under maternal characteristics.

2.2 Statistical Analysis

The Statistical package SPSS 20 was used for data analysis. Descriptive results are given as mean ± standard deviation (or median and range) or frequencies and percentages. Comparison of proportions was performed using the Yates' corrected chi-square test and *t* test for comparison of two means. *P*-values ≤ 0.05 were considered statistically significant.

3. RESULTS

Fifty-nine pregnancies following ART were managed in our hospital during the period under review. Four of the pregnancies were not carried to foetal viability (miscarriages) so were excluded from the analysis. Out of the 55 viable pregnancies, 51 were concluded in our hospital while four cases were referred for delivery abroad on request. They were also excluded from the analysis thus giving a sample size of 51 pregnancies following ART. There were 21996 deliveries over the 8-year period giving an incidence of delivery following ART of 0.3%.

Table 1 shows the demographic characteristics of the women. The women in the ART group

had significantly lower parity than the control group.

Table 2 looked at the maternal characteristics peculiar to women in the assisted conception group. Female factor was the cause for infertility in 22 (50%), while male factor was the cause in 9 (20%).

Intracytoplasmic sperm injection was the type of assisted conception carried out for all the women. In addition, in 18 (35%) women donor eggs were used for the ICSI procedure (ovum donation). Sixteen (41%) women got pregnant with their first attempt and three embryos were transferred at a time in about half (53%) of the women.

Table 3 shows the maternal and neonatal outcome among the women. Early pregnancy bleeding, hypertensive disorders of pregnancy, pre term delivery, caesarean delivery, low birth weight, neonatal admission and perinatal deaths were significantly commoner in the ART group. The rates of antepartum haemorrhage, diabetes mellitus, postpartum haemorrhage, maternal death and birth asphyxia were not statistically different between the two groups.

Table 1. Socio-demographic characteristics

Characteristics	Assisted reproduction group (n=51)	Control group (n=51)	p-value
Mean age (years)	38.5±7.3	37.3±5.9	
Age range			
25-34	16 (31)	17 (33)	
35-44	23(45)	26 (50)	
45-54	12 (24)	8 (16)	
Parity			
0	36 (71)	23 (45)	
1+	15 (29)	28 (55)	0.02*
Educational status			
Primary	1(2.0)	0 (0.0)	
Secondary	7 (14)	7 (14)	0.603
Tertiary	43 (84)	44 (86)	

**Statistically significant ($p \leq 0.05$)*

Table 2. Maternal characteristics of assisted reproduction group

Characteristics	Number of patients (%)
Causes of infertility	**n = 44**
Male factor only	9 (20)
Female factor only	22 (50)
Combined male and female factor	13 (30)
Type of assisted conception	**n = 51**
Intracytoplasmic sperm injection (ICSI)	51 (100.0)
Conventional *in vitro* fertilization	0 (0.0)
*Ovum donation and ICSI	18 (35)
Number of attempts	**n = 29**
1	16 (55)
2	10 (35)
3	1 (3)
4	1 (3)
5	1 (3)
Mean cost of a single assisted conception cycle	$7,500 ± 2900
Number of embryos transferred	**n = 51**
1	3 (6)
2	8 (16)
3	27 (53)
4	12 (24)
5	1 (2)

**Eighteen women used donated ova for their ICSI*

Table 3. Maternal and neonatal outcomes

Outcome	Assisted reproduction group n (%)	Control group n (%)	OR	95% CI	p-value
Early pregnancy bleeding	9 (12)	0 (0)	-		0.03*#
Antepartum haemorrhage	3 (4)	1 (2)			0.902#
Hypertensive disorders of pregnancy	13 (17)	3 (6)	2.95	1.05-13.8	0.05*#
Diabetes mellitus	7 (9)	1 (2)			0.195#
Multiple pregnancy	24 (32)	3 (6)	5.44	1.45-24.0	0.001*#
Singleton	27(53)	48 (94)			0.001*
Twins	15 (30)	3 (6)			0.001*#
Triplets	7 (14)	0 (0)			0.01*#
Quadruplets	2 (4)	0 (0)			0.393#
Preterm delivery	16 (21)	1 (2)	10.88	1.44-66.1	0.002*#
Post partum haemorrhage	3 (4)	0 (0)			0.395#
Caesarean delivery	46 (90)	9 (17)	3.48	1.48-8.4	0.001*#
Maternal death	3 (6)	0 (0)			0.241#
Mean gestational age at delivery (weeks)	34.1 ± 7.9	38.6 ± 1.1			0.001*
Mean birth weight (kg)	2.62 ± 0.8	3.24 ± 0.5			0.001*
Low birth weight < 2.5kg	35 (44)	3 (6)	7.93	2.17-34.3	0.001*#
Apgar score < 7 @ 1st minute	10 (13)	3 (6)			0.176#
Neonatal admission in SCBU	18 (23)	4 (7)	3.06	1.90-11.4	0.02*#
Perinatal death	7 (8)	0 (0)	--		0.03*# -

**Statistically significant ($p \leq 0.05$) #Fishers exact*

4. DISCUSSION

Assisted reproductive techniques (ART) are a major breakthrough in the medical treatment for human subfertility. With the increasing use of ART in the past three decades, the number of infants born from ART has reached an estimated 5 million since the first ART baby was born in 1978 [24]. However, ART remains largely unavailable or inaccessible to majority of citizens of less resource countries. With failing fertility in some countries, the rates of births following ART are expected to rise [25]. Initially, increase in success rate of the ART procedure was the primary concern of fertility specialists, however with the rapidly increasing number of children born following ART, maternal, perinatal and neonatal outcomes have become emerging concerns.

The mean age of the women in our study group was 38 ± 7.3 years. This is slightly higher than the 35 ± 4.3 years reported by Ezechi et al but still buttresses the fact that older women present for ART as they would have sought unorthodox treatment elsewhere as well as delay by primary gynaecologists in trying other conventional treatment before referring them [4,8]. Also because of the high cost of the procedure, even when the patients are referred early, financial constraints may delay early presentation at an ART centre [8]. Female factor alone was the cause for infertility in 22 (50%) of the women. This is similar to findings in infertility clinics in Nigeria [26]. Our result could be explained by the fact that our women were older with diminished ovarian reserve, and had probably tried conventional ovulation induction with no positive result. This was further supported by the fact that a third of the women had donated ova used for the Intracytoplasmic sperm injection (ICSI) procedure. All the women had ICSI as the form of ART procedure. This is because it results in better pregnancy outcomes and most of the ART clinics in Port Harcourt carry out this process. It is also the recommended procedure for male factor infertility including severe oligoasthenoteratozoospermia (OATS).

The higher rate of multiple pregnancies in the ART group compared to the control group is similar to findings in other studies [15,27]. The main reason for the increased incidence of multiple fetuses is that multiple embryos are transferred. Due to the expensive nature of ART, couples employing IVF/ICSI may request

that more than one embryo be transferred in order to optimize the chances of achieving pregnancy with a single treatment. Indeed, we found that about half of the women we studied (53%) had three embryos transferred, as that was the policy of most ART clinics in Nigeria. This practice needs to be reviewed as the trend is moving to elective single embryo transfer to avoid the increased perinatal morbidity and mortality resulting from multiple gestation as well as the steep financial burden imposed on maternal and neonatal services. These ART centres should invest in cryopreservation facilities so that extra embryos are frozen for future rather than the dangerous practise of transfer of multiple embryos. Australia has been a world leader in single embryo transfer, with ART multiple birth rates of less than 6%. However, this is still higher than the rate in the general population of 1–2 per cent. [28]

The mean cost of a single assisted conception cycle in Nigeria from our study was $7,500 ± 2900. This is very expensive and beyond the reach of most Nigerians that require the procedures hence the preference for as many embryos as possible transferred at a time [29]. The government in Nigeria and indeed other African countries should undertake part financing of ART, as this will go a long way in reducing the exorbitant cost.

A meta-analysis and evidence check review of ART pregnancies suggested that such pregnancies are at increased risk for adverse complications such as antepartum haemorrhage, hypertensive disorders of pregnancy, placental abnormalities (placenta praevia, placenta accreta and placental abruption), gestational diabetes mellitus, preterm delivery, low birth weight and neonatal intensive care admission than non-ART pregnancies. They also have a significantly increased risk of caesarean section and a small increase in the incidence of postpartum haemorrhage [30,31].

This study found a higher incidence of preterm delivery among the assisted reproduction (ART) group compared to spontaneously conceived pregnancies. The higher incidence of preterm delivery in the ART group may be as a result of higher incidence of multiple pregnancies, which is a known cause of preterm delivery [8]. Hypertensive disorders of pregnancy was the commonest medical complication we encountered (17%) followed by gestational diabetes mellitus [GDM] (9%) However, though our rate for GDM was higher than the 3% reported in Sweden, [32] similar results were obtained in Kuwait. [33] It is suggested that GDM might be related to a high prevalence of polycystic ovary syndrome (PCOS) among infertile patients or to an ovulation stimulation agent [22].

Early pregnancy bleeding occurred in 12% of women in our study group. This is similar to reports from other studies [8, 20-21]. It is thought to be as a result of early antenatal surveillance, a higher incidence of placenta praeviae and preterm uterine contractions in IVF pregnancies. This is supported by our results, with the exception of placental complications that had a low incidence of 4%.

The high caesarean section rate among patients in the assisted conceptions group may not be unconnected with physician anxiety as well as the nature of the pregnancy. This high rate is not only related to the high incidence of multiple pregnancy but a consideration of duration of infertility, financial investment in the assisted conception, the patient's as well as the doctor's anxiety. The probability of a caesarean section is higher (x 1.2-1.5) in pregnancies conceived via IVF than spontaneous conception and this applies both with singleton and twin delivery [34]. The 3 maternal deaths in the ART group were due to 2 cases of primary post-partum haemorrhage and one acute pulmonary oedema - a complication of the severe pre eclampsia, giving a rate of 6%. There were no maternal deaths in the control group. Maternal deaths in our hospital generally are high. These deaths are mainly due to hypertensive disorders of pregnancy, obstetric haemorrhage, obstructed labour, sepsis and miscarriages. The causes of death in the ART group are similar to what obtains generally. Limited evidence has shown that maternal mortality during an ART pregnancy does not seem to be different from maternal mortality during spontaneously conceived pregnancy [31].

In this study, low birth weight, neonatal admissions and perinatal deaths were significantly commoner among the ART group. The higher neonatal admissions rate among the ART pregnancies compared to the control group was mainly due to prematurity. The overall perinatal mortality rate was 81 per 1000 live births in the study group and was also due to prematurity. This is higher than the rate reported

in a previous study but comparable with others. [20,21,33]

This is the first available evidence from a public hospital in Southern Nigeria comparing the outcome of ART pregnancies with spontaneously conceived ones. This study has shown that pregnancies following assisted conception are associated with more adverse outcomes probably due to the multiple numbers of embryos transferred thus resulting in multiple gestations with their associated complications.

Our study is limited by its retrospective nature and small size, which is due to the fact that most of the women who conceive following assisted conception would probably deliver in privately owned hospitals where the procedure was carried out initially. The absence of a national registry of ART births in Nigeria also makes comparison of results difficult.

5. CONCLUSION

Pregnancies resulting from assisted conception are associated with more adverse feto-maternal outcomes compared with spontaneously conceived pregnancies. The adverse outcomes are not unrelated to the fact that ART pregnancies result in higher incidence of multiple gestations with its attendant complications. As the numbers of ART conception and births in the country increase, a larger population size and a systematic review will be needed to confirm these findings. There is a dire need for a national registry for ART births and a strong regulatory body to make ART procedures more effective and safe.

CONSENT

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
http://sciencedomain.org/review-history/17678