Original Article

Factors Associated with Clinical Pregnancy following Assisted Reproductive Technology: A Comparative Cross-Sectional Study

Abstract

Background: Over the years, the numbers of centres performing assisted reproductive technology (ART) have increased in urban regions of Africa. We reviewed a 10-year record of ART in a public hospital in a bid to determine the pregnancy rate and identify factors associated with achieving clinical pregnancy. **Materials and Methods:** This was a retrospective, analytical, cross-sectional study of 604 women who had undergone *in vitro* fertilisation (IVF) or IVF/intra-cytoplasmic sperm injection, over a 10-year period, at the [Institute of Fertility Medicine, Lagos State University Teaching Hospital]. Data were obtained from the medical records of couples who had undergone IVF at the study location and analysed using relevant descriptive and inferential statistics. Regression analysis was used to determine possible predictors of clinical pregnancy outcomes at 95% confidence level and significant *P* value of <0.05. **Results:** The clinical pregnancy rate observed was 23.7%. Women aged ≥35 years of age had 2.9 odds of achieving pregnancy compared to women <35 years of age. The quality of embryo and dose of the follicle-stimulating hormone used were not significantly different when compared in pregnant and non-pregnant women (*P* = 0.612 vs 0.881). Endometrial preparation techniques, number of embryos transferred, types of embryos transferred, sperm quality, and source of gametes used were not significantly different in pregnant and non-pregnant women. There was a 0.77 odds of achieving pregnancy when a day-5 embryo was used compared to a day-3 embryo (*P* = 0.008). **Conclusion:** Overall, these results emphasise the multifaceted nature of IVF outcomes, urging further research to elucidate the intricate factors influencing success rates in assisted reproduction.

Keywords: *Assisted reproductive technology, ICSI, in vitro fertilisation*

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Introduction

Infertility affects 10%–32% of couples, with primary infertility responsible for 3% and the more common secondary infertility responsible for 5%–23%, which could be attributed to higher rates of infection-related tubal factor infertility in low- to middle-income countries.[1,2] It is estimated that more than 180 million couples in developing countries suffer from primary or secondary infertility.[3] Traditional and social pressures on infertile women in African countries may cause psychosocial distress.[4] "Fruitful expectations" put enormous burden disproportionately on African women suffering from infertility, and these unceasing pressures call for urgent intervention.[5] The considerable socio-cultural, psychological, and economic impacts of infertility on African women need to be alleviated by assisted reproductive technology (ART) and other appropriate alternatives.[6]

In 2001, the World Health Organization recognised infertility as a public health problem and recommended that ART be complementary to other ethically acceptable solutions to infertility.[7] The number of centres performing *in vitro* fertilisation (IVF) in Africa is increasing day by day, and currently African countries having the highest number of IVF centres are Egypt, Ghana, Kenya, Nigeria, and South Africa.[3] However, only few reports provide pregnancy or birth rates for large groups of infertile couples in these regions.[8]

ART refers to all treatments or procedures that include *in vitro* handling of human oocytes and sperm or embryos for the purpose of establishing a pregnancy. This includes, but is not limited to, IVF and transcervical embryo transfer, gamete intrafallopian transfer, zygote

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intrafallopian transfer, tubal embryo transfer, gamete and embryo cryopreservation, oocyte and embryo donation, and gestational surrogacy. ART does not include assisted insemination (artificial insemination) using sperm from either a woman's partner or sperm donor.[7]

Reported success rates have so far been fairly constant, at around 25% live births per cycle.[9] Vayena *et al*. on "current challenges in assisted reproduction success rate" in a WHO report stated that "a 25% success rate sounds good enough but also means a failure rate of around 75%, that is, distressing for those who went through the financial and heavy psychological cost of the procedure."[7] He asked "can we bring happiness to more couples and can we have better predictors of the outcome, to save those unfortunate couples from going through the heavy burden of the procedure if they have no chance of success?"[7]

Therefore, we reviewed a 10-year record of women who had ART in a public tertiary hospital in [in Lagos, Nigeria] to provide the success rate and identify possible demographic and clinical predictors of pregnancy following ART.

Materials and Methods

This was a retrospective, analytical cross-sectional study involving 604 women who had IVF or intra-cytoplasmic sperm injection, over a 10-year period, at the [Institute of Fertility Medicine, Lagos State University Teaching Hospital].

The medical records of couples desirous of conception who presented at the study location for IVF or intra-cytoplasmic sperm injection between January 2012 and January 2022 were reviewed for relevant study data.

Data pertaining to age, religion, parity, ethnicity, regularity of menstrual cycle, number of children alive, weight, height, stimulation protocol used, number of cycle attempt at oocyte retrieval, method of fertilisation (IVF or intra-cytoplasmic sperm injection), quality of embryos used, type of endometrial preparation before transfer, number and type of embryos transferred, sperm quality, gametes used (use of a donor for sperm and/or oocytes), and ART outcome were obtained.

Day-3 embryos were graded using three criteria: (1) number of cells; (2) symmetrical arrangements (A – equal size; B – mostly unequal size); and (3) fragmentation (1 – no fragmentation seen; 2 – minor/moderate fragmentation; 3 – heavy fragmentation).

Embryo grading on day-5 was performed using three criteria: (1) thinning/ expansion of the zona pellucida and liquid cavity (3 – early blast, 4 – full blastocyst, 5 – hatching, and 6 – hatched out from the zona); (2) inner cell mass (ICM) grows into the foetus (A – fully compacted into a ball shape; B – compacted into a cone-like shape; C – sparely/no compaction); and (3) the trophectoderm develops into the placenta (A – nicely populated; B – moderately populated; C – sparely populated).

The following embryos were classified as good-quality embryos: 3AA, 4AA, 5AA, 6AA, 3AB, 4AB, 5AB, 6AB, 4BA, 5BA, 6BA, 3BB, 4BB, 5BB, and 6BB, while poor-quality embryos included those with grades 4BC, 5BC, 6BC, 4CB, 5CB, or 6CB.

Clinical pregnancy in this study is defined as evidence of pregnancy by clinical or ultrasound parameters (ultrasound visualisation of a gestational sac).[7] It includes ectopic pregnancy. Multiple gestational sacs in one patient are counted as one clinical pregnancy.[7]

The data obtained were entered and analysed using the Statistical Package For Social Sciences (IBM Corp., Armonk, NY, United States), version 22. They were categorised into women who achieved clinical pregnancy and women who did not achieve clinical pregnancy. The chi square test or Fischer's exact test was used to determine the association of categorical variables. Regression analysis was used to determine possible predictors of clinical pregnancy outcomes. For all statistical tests, a confidence level of 95% was used, with $P < 0.05$ denoting statistical significance.

Results

One hundred and forty three of 604 women achieved pregnancy, giving a clinical pregnancy rate of 23.7% [Table 1]. Women aged 35 years and above accounted for 54.5% (78) of women who achieved a clinical pregnancy, and 73.1% (337) of the women did not achieve pregnancy ($P < 0.001$) [Table 1]. Most of the women who had IVF or ICSI were nulliparous, as 88.1% of women who achieved a clinical pregnancy and 90.2% of women without pregnancy did not have any previous parous experience ($P = 0.356$) [Table 1]. Fifty six (39.2%) of the 143 women who achieved a pregnancy and 186 (40.3%) of 461 women who did not achieve a pregnancy were overweight [Table 1]. There was no difference in the body mass index between women who achieved a pregnancy and those who did not ($P = 0.754$) [Table 1].

There was no significant difference in both the serum follicle-stimulating hormone (FSH) levels and dose of gonadotrophin (exogenous FSH) used in pregnant and non-pregnant women following ART. Both median serum FSH and anti-Mullerian hormone (AMH) level were similar in pregnant and non-pregnant women. Good-quality embryos were most frequently (83.2%) used in women who achieved a pregnancy compared to 16.8% of women, who had received poor-quality embryos but achieved clinical pregnancy [Table 2]. The quality of embryos used was not significantly different when compared in pregnant and non-pregnant women ($P = 0.612$) [Table 2]. The endometrial preparation technique, number of embryos transferred, types of embryos transferred, sperm quality, and source of gametes used were not significantly different in pregnant and non-pregnant women [Table 2].

Table 1: Comparison of demographic and clinical characteristics based on the outcome

Variables	Pregnant *n* = 143 (23.7%)	Not pregnant *n* = 461(76.3%)	χ^2	*P* value
Age group (years)			17.481	<0.001
<35	65 (45.5)	124 (26.9)		
≥35	78 (54.5)	337 (73.1)		
Mean ± SD	*36.3 ± 6.3*	38.1 ± 6.2	-3.091	0.002
Religion			0.586	0.444
Christianity	113 (79.0)	350 (75.9)		
Islam	30 (21.0)	111 (24.1)		
Tribe			1.966	0.557
Yoruba	119 (83.2)	358 (77.7)		
Igbo	21 (14.7)	89 (19.3)		
Hausa/Fulani	0 (0.0)	2 (0.4)		
Others	3 (2.1)	12 (2.6)		
Parity			2.117[f]	0.356
0	126 (88.1)	416 (90.2)		
1	15 (10.5)	33 (7.2)		
≥2	2 (1.4)	12 (2.6)		
Menstrual cycle			3.167	0.075
Regular	119 (83.2)	351 (76.1)		
Irregular	24 (16.8)	110 (23.9)		
Number of children alive			0.439	0.507
0	129 (90.2)	424 (92.0)		
1–3	14 (9.8)	37 (8.0)		
BMI class			1.211[f]	0.754
Underweight	1 (0.7)	6 (1.3)		
Normal	48 (33.6)	134 (29.1)		
Overweight	56 (39.2)	186 (40.3)		
Obese	38 (26.6)	135 (29.3)		

χ^2: chi square test
[f]Fischer's exact test applied

There was 2.9 times higher likelihood of achieving pregnancy in women aged 35 years and above compared to women aged less than 35 years of age [Table 3]. The use of grade 2 embryo was 2.4 times more likely to result in pregnancy than that of grade 1 embryo ($P = 0.073$). There is a 0.77 odds of having a pregnancy with the use of a day-5 embryo compared to the use of a day-3 embryo ($P = 0.008$) [Table 3]. Table 4 shows the correlation between age, quality of embryo, and type of cycle.

Discussion

Firstly, the constant success rate of assisted reproduction is vital when counselling couples seeking to attempt IVF.[9] However, the larger proportions of women who experience failure, despite huge financial investment, are further distressed, especially in developing countries.[7] In this review of a 10-year ART record, we found a clinical pregnancy rate of 23.7% of initiated cycles following IVF/ICSI, probably due to an obviously smaller sample size (24). Makwe *et al*.[10] in Lagos, Nigeria, reported a higher clinical pregnancy rate of 33.3% (8/24) per initiated cycle in a similar study. Only very few published reports on IVF/ICSI success rates of large population are readily available in Nigeria. Pierce *et al*.[11] reported a clinical intrauterine pregnancy rate of 26% for women aged 35–39 years. More than two-thirds of women in our study were 35 years of age and above. This may explain why the pregnancy rate of 23.7% in our study is slightly comparable with the rate of 26% reported by Pierce *et al*. among women aged 35–39 years.

About two-thirds (68.7%) of the women (415/604) who underwent IVF/ICSI were aged 35 years and above with a mean age of 37.7 years. Pierce *et al*. noted that the mean age of a woman receiving IVF treatment in the United Kingdom was 35 years, which was comparable to 36 years in the United States.[11-13] The mean age of 37.7 years in our study is similar to these UK and US reports. Furthermore, the Human Fertilisation and Embryology Authority reporting a mean age of 34.8 years for woman seeking fertility treatment, as of 2004, suggests that more older women are opting for IVF.[14] Age was significantly different ($P < 0.001$) when comparing pregnant with non-pregnant women; on the other hand, parity and BMI were similar in both groups of women.

We observed that less than one-tenth (6.3%) of our study population, during the study period, had more than one IVF cycle despite not achieving pregnancy. We suppose that the relatively low occurrence of repeated IVF cycles

Table 2: Comparison of IVF cycle characteristics based on the outcome

Variables	Pregnant *n* = 143 (*r* %) [c %]	Not pregnant *n* = 461(*r* %) [c %]	χ^2	*P* value
Number of IVF cycles				
1	130 [90.9]	438 [95.0]	3.276	0.070
>1	13 [9.1]	23 [5.0]		
Serum FSH level (U/L)				
Low	1 (1.3)	3 (1.4)	0.254[f]	0.881
Normal	73 (91.3)	204 (92.7)		
High	6 (7.5)	13 (5.9)		
Median FSH (IQR)	*7.8 (6.4–10.5)*	*8.2 (1.9–75.4)*	*-0.447*[m]	*0.655*
Median AMH (IQR)	4.3 (1.1–17.9)	6.3 (1.4–17.5)	-0.884[m]	0.377
Dose of FSH used (IU)				
≤150	31 (23.7)	85 (24.5)	0.096	0.953
225–300	79 (60.3)	210 (60.5)		
>300	21 (16.0)	52 (15.0)		
Quality of embryo used			12.130[c]	<0.001
Good	131 (26.5) [91.6]	363 (73.5) [78.7]		
Poor	12 (10.9) [8.4]	98 (89.1) [21.3]		
Quality of embryo in donor cycle			6.731	0.009
Good	52 (26.5) [94.5]	144 (73.5)		
Poor	3 (7.5) [5.5]	37 (92.5)		
Quality of embryo in self-cycle			5.807	0.016
Good	79 (26.5) [89.8]	219 (73.5) [78.2]		
Poor	9 (12.9) [10.2]	61 (87.1) [21.8]		
Endometrial preparation before transfer			2.038[f]	0.545
Day-2 down-regulation	4 (2.8) [20]	16 (3.5) [80]		
Day-21 down-regulation	131 (91.6) [23.4]	428 (92.8) [80.3]		
Not done	1 (0.7) [50]	1 (0.7) [50]		
Others	7 (4.9) [30.4]	16 (3.5) [69.6]		
Number of embryo transferred			2.115[f]	0.491
0	0 (0.0) [0.0]	2 (0.4) [100]		
1	3 (2.1) [12.5]	21 (4.6) [87.5]		
2	138 (96.5) [24.2]	433 (93.9) [75.8]		
≥3	2 (1.4) [28.6]	5 (1.1) [71.4]		
Type of embryo transferred			4.909[f]	1.103
Day-3 embryo	8 (5.6) [13.6]	51 (11.1) [86.4]		
Day-5 embryo	134 (93.7) [24.7]	409 (88.7) [75.3]		
Frozen embryo	1 (0.7) [50]	1(0.2) [50]		
Sperm parameters			3.281[f]	0.489
Normal	44 (26.8) [30.8]	120 (73.2) [26.0]		
Oligospermia	95 (23.2) [66.4]	314 (76.8) [68.1]		
Azoospermia	3 (10.7) [2.1]	25 (89.3) [5.4]		
Teratozoospermia	1 (33.3) [0.7]	2 (66.7) [0.4]		
Gamete used			1.388	0.239
Donor	48 (33.6) [26.8]	131 (28.4) [73.2]		
Patient	95 (66.4) [22.4]	330 (71.6) [77.6]		
Age of donor cycle women (years)				
<35	14 (41.2) [25.5]	20 (58.8) [11.0]	7.098	0.008
≥35	41 (20.3) [74.5]	161 (79.7) [89.0]		
Age of self-cycle women (years)				
<35	51 (32.9) [58.0]	104 (67.1) [37.1]	11.896	0.001
≥35	37 (17.4) [42.0]	176 (82.6) [62.9]		

χ^2: Chi square test, ( ): column percentage, [ ]: row percentage, IU: international units, U/L: units per litre, AM: anti-Mullerian hormone, IQR: interquartile range
[m]Mann–Whitney *U* test applied
[f]Fishers exact test applied

Table 3: Predictors of pregnancy in women seeking assisted conception

Variables	aOR	95% CI odds ratio	*P* value
Age group (years)			
<35	Reference		
≥35	2.863	1.799–4.556	0.000
Body mass index			
Obese	Reference		
Underweight	2.710	0.304–24.187	0.372
Normal	0.787	0.463–1.337	0.375
Overweight	0.908	0.550–1.498	0.705
Stimulation protocol			
Agonist short protocol	Reference		
Antagonist protocol	0.312	0.053–1.853	0.200
Long protocol	0.431	0.095–1.963	0.277
Number of cycle attempt at oocyte retrieval			
1	Reference		
2	0.424	0.182–0.986	0.046
≥3	1.067	0.104–10.938	0.956
Method of fertilisation			
Intra-cytoplasmic sperm injection	Reference		
In vitro fertilisation	1.660	0.318–8.669	0.548
Spouse's sperm parameters			
Normal	Reference		
Oligospermia	1.432	0.914–2.242	0.117
Azoospermia	3.157	0.873–11.416	0.080
Teratozoospermia	1.103	0.069- 17.656	0.945
Quality of embryos used			
Poor	Reference		
Good	0.780	0.459–1.324	0.357
Type of embryo transferred			
Day-3 embryo	Reference		
Day-5 embryo	0.233	0.079–0.681	0.008*
Frozen embryo	0.226	0.008–6.668	0.389
Type of cycle			
Donor cycle	Reference		
Patient's own cycle	0.710	0.320–1.573	0.398
Gamete used			
Donor	Reference		
Self	2.531	1.111–5.766	0.027*

aOR: adjusted odds ratio

Table 4: Relationship between age, quality of embryo, and type of cycle

Variables	Quality of embryo		χ^2/Fisher's exact	*P* value
	Good, *n* (%)	Poor, *n* (%)		
Donor cycle				
Age group (years)			0.077	0.781
<35	18 (90.0)	2 (10.0)		
≥35	146 (91.8)	13 (8.2)		
Patient's own cycle				
Age group (years)			10.742	0.001
<35	145 (85.8)	24 (14.2)		
≥35	185 (72.3)	71 (27.7)		
Over all				
Age group (years)			3.666	0.068
<35	163 (86.2)	26 (13.8)		
≥35	331 (79.8)	84 (20.2)		

in our study may be attributed to the financial implications involved. Patients seeking assisted conception often bear the financial burden out of pocket.

This study revealed that use of poor-quality embryos for IVF/ICSI resulted in less than one-fifth (16.8%) of the women achieving clinical pregnancy, which is in consonance with the findings by Ziebe *et al*.[15] Four in five of the women (83.2%) who got pregnant had received good-quality embryos during their ART procedure. Therefore, the general consensus that better-quality embryos result in improved pregnancy chances,[16] is further buttressed by our findings and also true in an African population. However, we cannot ignore the fact that 80% of good-quality embryos accounted for over 80% of women not achieving clinical pregnancy. Further regression analysis in Table 3 showed that embryo quality was not significantly associated with clinical pregnancy. The retrospective design of this study might have limited its ability to establish causation and control for potential confounders and biases. Similarly, the endometrial preparation technique, number of embryos transferred, types of embryos transferred, sperm quality, and source of gametes used were not significantly different in pregnant and non-pregnant women.

On the other hand, we observed that women aged 35 years and above were 2.9 times more likely to achieve clinical pregnancy following IVF or ICSI when compared with women less than 35 years of age. This discovery does not agree with the common trend. Generally, as regards the impact of women's age on IVF outcomes, rates of pregnancy and live birth decline as a woman's age increases.[11,17,18] Grøndahl *et al*.[17] reported 40% IVF success rate in women between 25 and 29 years of age, 32% in those aged 35–39 years, and 17% of those aged 40–46 years. This disparity with our findings may be partly attributable to the predominant use of donor oocytes in women aged 35 years and above compare to women aged less than 35 years. In the study centre, donated oocytes were usually from young women between age 20 and 25. However, further sub-analysis, which involved categorising women into donor and self-cycles (Table 2), revealed a notable age difference between those who achieved pregnancy and those who did not, even after accounting for the use of donor eggs. This buttresses the fact that attributing higher pregnancy rates to the use of donor eggs in women aged 35 years and above does not fully account for the observed disparity. Furthermore, the number of women utilising donor eggs was relatively small compared to the cohort of women aged 35 years and above. Consequently, caution should be exercised in generalising this finding, and interpretations should be made with consideration of the age distribution of our study population.

Furthermore, in our population, we observed 0.77 odds of having a pregnancy when a day-5 embryo was transferred compared to use of a day-3 embryo. However, the results of previous randomised clinical trials and retrospective observations that examine transfer of day-3 compared to day-5 embryos have been variable and inconsistent.[19-22] Garbhini *et al*.[23] in Indonesia noted that transfer of neither day-3 nor day-5 embryo showed any significant differences in clinical pregnancy or implantation rates. Hatırnaz and Kanat Pektaş[24] following a randomised controlled trial in Turkey also reported that the efficacy of blastocyst-stage embryo transfer is not inferior to that of cleavage stage embryo transfer. We believe that variations in the characteristics of the patient population in our study compared to those in other studies could play a role in the discrepancy with our study findings. In addition, more than four-fifths of the women in this study had day-5 embryo transfer. Factors such as age, study design, and differences in patient demographics may also have been contributory.

Overall, these results emphasise the multifaceted nature of IVF outcomes, urging further research to elucidate the intricate factors influencing success rates in assisted reproduction.

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Ethical approval and consent to participate

Ethical approval for the study was obtained from the Health Research and Ethics Committee of the Lagos State University Teaching Hospital (LASUTH) with protocol number LREC/06/10/1887.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analysed during the current study are available in the Mendeley Data repository (doi:10.17632/kkpb82dp3x.1).

Author contributions

TAO, AAA, and FOJ conceived the study and managed and performed the artificial reproductive techniques on the patients. AMO analysed and interpreted patient data. TAO, AAA, and AMO were major contributors in writing the manuscript. All authors read and approved the final manuscript.

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Nil.

Conflicts of interest

There are no conflicts of interest.

List of Abbreviations

AMH Anti-Mullerian hormone
ART Assisted reproductive technology

ASRM American Society of Reproductive Medicine
BMI Body mass index
FSH Follicle-stimulating hormone
HFEA Human Fertilisation and Embryology Authority
ICM Inner cell mass
ICSI Intra-cytoplasmic sperm injection
IVF *In vitro* fertilisation
SART Society for Artificial Reproductive Technology
UK United Kingdom
US United States
WHO World Health Organization

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