

Intrauterine in vivo fertilization: low cost and low tech management of tubal factor infertility

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Summary

Ten to 30 percent of Nigerian couples suffer from infertility at one point in their life. Tubal factor infertility accounts for about 20% of infertility. It is managed currently with in vitro fertilization (IVF) when the two tubes are blocked. Eight couples with exclusive bilateral tubal blockage in the female partners were recruited for intrauterine gametes transfer (IUGT) for possible intrauterine in vivo fertilization as a cheaper alternative to IVF. Only five patients out of the eight recruited had IUGT but none achieved pregnancy.

Key Words: Intrauterine; Gametes transfer; Tubal infertility.

Introduction

Infertility is a problem of couples worldwide with the highest prevalence in low income countries, especially in sub-Saharan Africa where tubal disease from pelvic infections is a major cause. Though not life threatening, it is a major cause of social and psychological distress to the couples in this part of the world where a marriage without a child is often regarded as a failure [1]. Assisted conception remains the mainstay of treatment for couples with tubal disease but this remains beyond the reach of most couples because of cost and accessibility. There is therefore the need for the development of low cost procedures like in vivo intrauterine gametes transfer (IUGT) where less sophisticated equipments, less materials, and media are used for fewer numbers of days.

Problem statement and specific objectives

Tubal disease accounts for a significant proportion of female factor infertility in Nigeria and other developing countries world due mainly to poor prevention and management of ascending pelvic infections, especially sexually transmitted infections. Human reproduction naturally involves joining of male gamete (spermatozoon) and female gamete (ovum) in the fallopian tube (in vivo salpingo fertilization); however if the two female tubes become blocked or diseased then definite treatment available is to bypass the fallopian tubes by way of outside fertilization (in vitro fertilization-IVF) or recourse to tubal surgery. Tubal surgery yields poor results and has been virtually abandoned for IVF [2].

The cost of IVF is presently unaffordable by majority of Nigerians. IVF involves inducing ovarian hyperstimula-

tion, egg retrieval and preparation, semen preparation, IVF and culture, followed lastly by embryo transfer into the female womb. This implies use of complex and detailed laboratory processes involving use of expensive equipment like stereozoom microscope, Laminar flow work station, air filters, carbon dioxide incubator, and specially designed laboratory which mimics sterile environment of female internal pelvic organs. The cost of equipping this laboratory is exorbitant and laboratory skills required are not being taught in any of Nigerian Universities for now. Thus evolving a low tech and low cost technique which requires less technical laboratory procedures with fewer and less costly equipments that can be made available in many public health facilities is highly desirable.

The objective of this experimental research is to use in vivo mixing of human gametes placed in the uterus (in order to produce pregnancy) to treat bilateral fallopian tubal blockage. The specific objective was to determine if intrauterine placement of human gametes can lead to fertilization and implantation of embryo. The research location included Department of Obstetrics & Gynaecology, College of Health Sciences, LAUTECH, Isale Osun, Osogbo. It has 11 full time lecturers that double also as researchers, a Professor, and two readers inclusive.

LAUTECH Teaching Hospital (LTH), Osogbo has eight clinical consultants in Obstetrics & Gynaecology. It receives patients as referrals from government general hospitals, Comprehensive health centres, private hospitals in and out of Osun States. It has 12 gynaecological beds for admission. Dr. J.O. Komolafe was the anchor researcher in

this study for LTH, Osogbo.

LTH, Ogbomoso, has seven clinical consultants in Obstetrics & Gynaecology. It receives patients as referrals from government general hospitals, comprehensive health centres, private hospitals in and out of Ogbomoso, and other parts of Oyo States. It has 30 gynaecological beds for admission. Dr. A.M. Tijani was the anchor researcher in this study for LTH, Ogbomoso.

Ayomide Women's Health Specialist Hospital, Osogbo. Located at 2nd Gate, Power Station, Ikirun road, Osogbo. It offers assisted reproductive technology (ART)/ IVF. Dr. Komolafe provided link to make the IVF laboratory available for use.

Materials and Methods

Subjects included couples who have been unable to achieve pregnancy after at least one year of having unprotected and adequate sexual exposures. The male partners on assessment were required to have normal semen parameters using World Health Organization bench marks. The female partners needed to have both fallopian tubes blocked following use of hysterosalpingography (HSG) or laparoscopy. All other reproductive parameters in the female partners were required to be normal. The female had to be less than 36 years of age. Subjects were drawn from three clinical locations mentioned above. Only the first ten couples that met above inclusion criteria were recruited in order to stay within the approved budget for this study.

Design details included Phase 1: recruited patients were started on daily combined oral contraceptive pills at a pre-determined time for four weeks. This caused them to have withdrawal bleeding (menses) at about the same time so they were followed up at the same time. All the women were started on buserelin 0.5 ml daily five days to expected day of menses and continued until one day before administration of human chorionic gonadotrophin (hCG). Fifty mg of clomiphene citrate tablet was given daily for seven days from a pre-determined day (2nd or 3rd day of withdrawal bleeding as applicable to particular patient). They were also given intramuscular injection of follicular stimulating and luteinizing hormones 150 I.U from 3rd day of menses for eight to ten days of menses in order to induce some hyperstimulation of egg production. They were monitored with transvaginal ultrasound from day 8 of menses and on alternate days. Once there were at least two follicles with diameter of greater or equal to 18 mm, an injection of hCG 10,000 I.U. was given to mature the eggs causing them to be released. Thirty-four hours after hCG administration, follicular aspiration was performed under conscious sedation and guided with transvaginal ultrasound. Oocytes were identified in the follicular fluid with the use of stereozoom microscope. Oocytes identified for each recruit were placed in petri dishes and layered with G mops media; they were subsequently transferred into the

incubator and left for two hours to allow oocytes complete 1st meiotic division with extrusion of 1st polar body. Subsequently two oocytes were taken from the candidates from their dishes and were loaded along with washed semen of corresponding male partner into soft pass embryo transfer catheter. Content was then emptied into the uterine cavity. Candidate was made to remain in lithotomy (with head down) position for one hour after intrauterine gametes insemination. Subsequently she was free to go home. All candidates were commenced on dydrogesterone one tablet (10 mg) daily from IUGT day until 20th day post-gametes transfer when serum pregnancy test was performed if patient had not seen menses.

Results

Ten Subjects that met the inclusion criteria were initially recruited and counseled. Two subjects were dropped as it became clear that the funding available would not be able to accommodate all the ten recruits. At the point of commencement of medications, one of the subjects called to opt out of study as her husband changed his mind on the study. Another woman of the remaining seven did not see her menses following initial medications and was found to be pregnant. She also was excluded automatically leaving only six patients that continued with study.

One of the six patients that had complete medication did not produce any follicle (egg) as monitored by transvaginal ultrasound scanning. The remaining five had follicular aspiration done yielding four, three, three, two, and one egg, respectively. They had intrauterine gametes placement as described in protocol.

All the patients saw their menses before the preset date for pregnancy test. One of them whose bleeding was scanty and presented for pregnancy test, tested negative for pregnancy.

Discussion

Fertilization occur in humans in the ampullary region of the fallopian tubes. It is the fertilized egg (embryo) that enters the uterus (womb) for implantation after about five days of life. The study sought to find an alternative location of fertilization in vivo for patients whose tubes were blocked or cut because of previous surgery. Study found alternative location however out of the human body over three decades ago, the so called test-tube babies (IVF) where the gametes were placed in a dish in the laboratory and were incubated at body's temperature until 3rd or 5th day of embryo life before replacing embryos back into the uterus.

One of the patients did not ovulate despite taking similar medications as the other patients. She claimed that her age was 34 years. A woman who was less than 36 years should produce at least one egg in natural unstimulated cycle. For her not to have any indicates she was probably older than

her claim. The authors have seen a case of a 44-year-old lady with a small build presenting as egg donor (an egg donor should be less than 33 years) and starting medications as donor only to confess her true age after initial administration of medications, but her ovaries showed no follicular activity. The authors did not insist on patients bringing birth certificate though some were disqualified by their facial aspect. This woman had a good build and managed to be included. Another possible reason was that she had poor ovarian reserve, although she was still menstruating normally. Women empty their ovarian (egg) pool at different rates [3].

None of the five patients that had intrauterine gametes transfer achieved pregnancy. The small number of participants as dictated by the available grant may be a factor since the authors know that reproduction in humans is rather inefficient, and among the best couples it is expected that only one pregnancy among five couples in a month i.e 20% with most average couples achieving one pregnancy after six months of regularly attempting to achieve one. It could also signify that the endometrial lining is not conditioned for fertilization. Scientists speak of receptive window of the endometrium which is said to be narrow & only occurring from 6th to 7th day following ovulation [4]. Despite this theory, pregnancy has been recorded when embryos were transferred into the uterus on day 2 of embryo life (3rd day from ovulation). It indicates that we might need to study the endometrium more closely to know how to adapt it so that it can be an alternative location for gamete fertilization in couples whose fallopian tubes have been blocked by infection or surgeries or endometriosis. Another factor to consider is the protocol used. Only two eggs were placed with appropriate number of motile sperm cells back into the uterus. Naturally only one egg is released usually, and to avoid the risk of multiple pregnancy of higher orders, egg transferred was limited to only two. Perhaps another protocol can attempt placing four or six eggs since we are aware of phagocytic leucocytes in the endometrium that would attack weak or morphologically abnormal sperm cells (e.g large head sperms); it could be that the eggs are phagocytosed by the leucocytes erroneously viewed as immotile and weak sperm cells.

Lastly, we must consider measures to ensure that the transferred gametes do not just flow back out of uterus as the tube is withdrawn from uterus. The isthmo-ampullary junction via a physiological valve retains the egg for some

time to allow interaction with the sperm. Although transfer tube was checked for attachment of egg after the transfer, there was no way of checking if the eggs flowed back into the vagina and then out subsequently.

Conclusions

No pregnancy resulted after IUGT among five patients included. Only one of the three set objectives could be tested due to limitation of research grant. Number of patients was too few to draw conclusive statement.

The results of this work should be adopted as a starting point in the quest for the development of a low cost procedures like in vivo intrauterine insemination of gametes where less sophisticated equipment, expensive materials, and media are used. More subjects should however be recruited in follow up studies.

This study showed that if two oocytes along with washed semen are transferred into the uterus, it may not result in pregnancy indicating that more procedures would have to be performed to achieve fertilization and implantation.

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