Assisted reproduction laboratory cost-drivers in South Africa: value, virtue and validity

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Abstract
An overview is given on selected cost-drivers within an assisted reproduction technology (ART) laboratory, such as procedural costs; sperm preparations; laboratory supplies including embryo culture media and cryopreservation. Depending on the nature of an ART unit, i.e. private vs. public/tertiary, the structure of the unit will differ with regards to costs, services offered, and general patient population. ART laboratory equipment, culture media and disposables are imported from various parts of the world to South Africa. Costs will be influenced by the choice of ART diagnostic and therapeutic techniques, disposables and devices, whereby laboratory costs can escalate to near 50% of ART fees payable in the private sector. The ultimate goal of an ART treatment should be to achieve a healthy singleton as cost effectively as possible, especially in a developing country.

Background

''We believe that civilization has been created under the pressure of the exigencies of life at the cost of satisfaction of the instincts. *Sigmund Freud*''.

The strength of desire to have a child can be reflected in motives such as happiness, well-being (family relationships), identity, parenthood (life-fulfilment), social control and continuity.[1] Parenthood-motives may differ among men and women, societies and cultures; but education, possessions, wealth or the lack thereof, will not change the desire for a biological child. If assisted reproduction technology (ART) services are solely provided in the private sector, then the treatment can be viewed as an elitists' prerogative to be assisted to have children, i.e. those that can afford the costs related to the procedures. Alternatively, one could argue that if state subsidies are applied to pay in full or partially for ART, then the taxpayer's contribution is used to benefit only a selected few with funds that could have been allocated to high priority health problems such as HIV/AIDS.[2] Living in Sub-Saharan Africa however, has a high probability to append HIV together with limited resources, to the barriers in becoming a parent. Resources available could influence the range of fertility screening and concurrent diagnostic and therapeutic health care decisions, which include scheduling for intra-uterine inseminations (IUI), in vitro fertilization (IVF) and intra-cytoplasmic sperm injection (ICSI), combined with semen decontamination for HIV-seropositive males.

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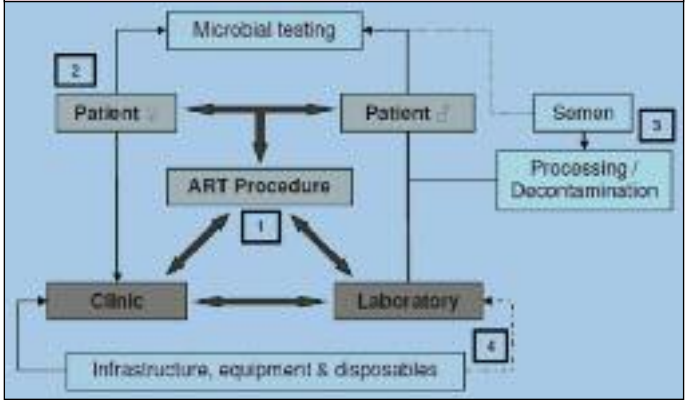
Ombelet et al. noted that if the diagnostic work-up of an ART program is simplified, then a larger part of the population in developing countries will have access to reproductive health care.[3] Questionnaires can for example construct the patient's history, and a clinical examination and screening for major infectious diseases can have a reasonable price tag for the couple. Using simple and accessible techniques such as office mini-hysteroscopy, hysterosalpingography and/or hystero-salpingo-contrast-sonography to diagnose tubal and uterine abnormalities, together with a basic semen analysis before and after processing, can provide valuable information on expected treatment to follow.[3] Certain cost-drivers of ART programmes, with emphasis on current laboratory set-up and procedures, in South Africa will be outlined in this review (see Figure 1), i.e. procedural costs, detection and

Figure 1: Selected cost-drivers of ART programmes: (i) procedural factors (ii) microbial screening, (iii) sperm preparations, (iii) facilities and supplies.



prevention of infections, sperm preparations, and laboratory facilities, including supplies needed to perform procedures.

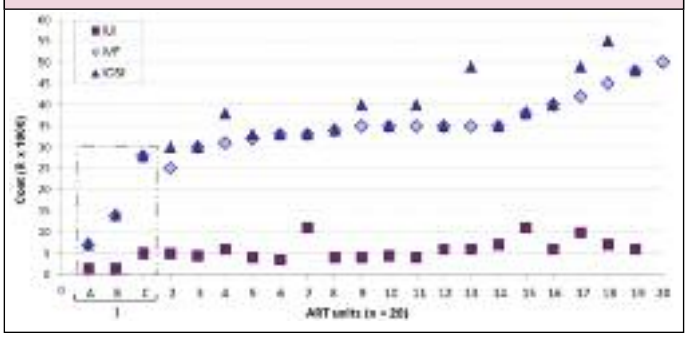
ART procedures

In 1982, the first ART units were established in South Africa, both tertiary institutions being situated in Pretoria and Cape Town.[4] Over the past three decades, the number has increased to approximately 27 ART service providers throughout South Africa, with most located within the private sector (cross-referenced with known providers in provinces and www.ivf-worldwide.com). Depending on the nature of a unit, i.e. private vs. public/tertiary, the structure will differ with regards to costs, services offered, and general patient population. Sallam suggests that within a developing nation, three levels of ART service should exist; (i) Level 1: a basic infertility clinic, offering basic semen analysis, hormonal assays, follicular scanning, ovulation induction and IUI, (ii) Level 2: an advanced infertility clinic offering in addition to level 1 services, diagnostic endoscopy as well as IVF, and (iii) Level 3: a tertiary level infertility unit, offering services in level 2, as well as operative endoscopy, ICSI and cryopreservation.[5] The Reproductive and Endocrine Unit, as part of the Department of Obstetrics and Gynaecology is a tertiary level infertility clinic combined with a laboratory, situated in Gauteng, providing both diagnostic and therapeutic procedures, including cryopreservation.[6] Apart from patient services, the laboratory is also a training facility for scientists and clinical technologists who are involved in academic research on various levels. The majority of patients attending the ART program at the unit are from the lower to middle income groups, however it is interesting to note that those patients that complete an ART attempt have an average household income of R16,700 ± R11,500 per month (random sampling of 50 patients whom completed an ART cycle).

Three different ART cost structures have recently been implemented at the unit, i.e. (A) an affordable low cost option, based on the recent drive for accessible IVF[3,7,8], (B) couples without medical aid and an annual income of less than R50,000 per household, is subsidized for an ART procedure, (C) couples with a medical aid and/or an income above R100,000 p.a. will be classified as "private" patients. The latter mentioned patients can also choose to access the low cost option, but need to comply with criteria based on aetiology, age and case history. Only a small budget is available per year, to assist a few patients who qualify for a subsidy in category B. The present patient ratio for these three cost categories is 1: 1: 6 patients (categories A to B to C, respectively). ART unit "1" represents the above-mentioned three cost structures (A-C), excluding costs for cryopreservation. The approximate costs (including medication, clinical-, pathology- and laboratory fees) per category are: **category A (affordable low cost option)**: R1,500 out-of-the pocket payment for a couple for an IUI attempt and up to R7,000 for an IVF or ICSI cycle; **category B (subsidized option, only registration fees, and no other fees payable by the couple)**: actual costs are R1,500 for IUI procedure and R14,000 for IVF or ICSI procedures; **category C (private option)**: up to R5,300 (case-dependent) payment for IUI procedure and up to R28,000 for IVF or ICSI procedures. Category B can also revert to fall within category A (low cost ART). Dyer and Kruger also referred to out-of-pocket costs of R10,000 (public sector subsidized) and R35,000 for a standard IVF cycle (within the private sector) in South Africa, which reflect the previous mentioned fee structure.[9]

The average costs for procedures from 19 private South African ART units (most from Gauteng), were obtained telephonically (April – June '12), and with the costs indicated in Figure 2 (no 2-20). Cost estimations (including medications, ultrasound scans and laboratory fees) were obtained for a standard IUI, IVF and ICSI procedure, except for a single unit (no. 20), which provided costs for only an IVF cycle and according to their policies will disclose full costs upon consultation. IVF procedures escalate from a minimum of R25,000 to R50,000 with ICSI costs similar or slightly higher in the private sector. The average fees per procedure (standard deviation (±)) in the private sector are (i) IUI: R6,083 ± R2,371 (ii) IVF: R36,368 ± R6,237 and (iii) ICSI: R38,611 ± R7,204. The average percentage of the major cost-drivers of a IVF cycle within a relatively large private practice, were given as: 8% of costs allocated for clinic fees, 28% to medication, 29% to clinicians' fees & consultations, and 35% for laboratory fees (for use of equipment and the laboratory, disposables, media and manpower). When comparing IVF to ICSI expenses, the ratio allocated to laboratory fees can increase by 13%. It is well known that IUI can be viewed as the most cost-effective ART procedure.[10] The proportioned costs for medication needed for an IUI cycle can be as low as 8% of the total expenses, compared to 23-28% for an IVF or ICSI cycle. This information was graciously provided by one of the largest ART units in South Africa. Although these components are the major cost-drivers in an ART unit, they are devised of smaller elements that are influenced by the purpose of a particular unit and its clientele. Chambers et al. is of opinion that "the cost of (ART) treatment reflects the costliness of the underlying healthcare system rather than the regulatory or funding environment." For full details on the economic impact of ART treatment, including affordability, cost-effective ratios and the cost of a standard IVF cycle in selected developed countries, see a review by Chambers et al.[11] Within South Africa, the out-of-pocket costs of ART procedures, limited health insurance coverage

Figure 2: Costs estimates for ART procedures for a public sector unit (no 1 A – affordable low-cost option, B – subsidized and C – private patients), and 19 private sector ART units.



of ART procedures, restricted access to a few ART units within the public sector and one may add, lack of appropriate funding to public sector ART providers.[9]

Screening of patients for pathogens: detection and prevention

The workup of couples prior to ART treatment and processing of human bodily fluids during procedures is standard for all patients, irrespective of the type of ART procedure. Finances available will possibly influence the couple's preference to visit a private or public service ART unit. This will also impact on the scope and frequency to screen for sexual transmitted infections, as well as the selection of ART procedures in lower to middle-income countries. Screening of the couple should however, be directed by the prevalence of the disease in the specific patient population, medical history and physical examination of the couple.[12] Semen and vaginal secretions can harbor various viral agents (cytomegalovirus (CMV), hepatitis B, C, D (HBV, HCV, HDV), herpes simplex virus type 2 (HSV-2), human T-lymphotrophic virus (HTLV), and human immunodeficiency virus (HIV)) that can be transmitted to the health worker, partner or potential offspring.[12]

In context to South African ART units the following questions can be asked: With the prevalence of HIV in Sub-Saharan Africa, should all patients who embark on an ART procedure be screened/re-screened for blood borne viruses (BBV)? Various bacteria-species are present in approximately half of all semen samples obtained for diagnostic or therapeutic ART procedures, with gram-negative species present in only a fraction of samples;[13] should all semen samples be submitted for bacteriological culture and sensitivity for diagnostic purposes? Should all patients receive prophylactic or empiric anti-microbial treatment options, with concurrent costs?

In the absence of a South African technical directive regarding the screening and treatment of ART patients for BBV/pathogens, we can gain insight in the requirements of the European Union Tissue and Cells Directives (EUTCD) (www.eur-lex.europa.eu) for ART Units in the EU, whereby ''biological screening must be carried out at the time of donation'' i.e. of sperm or oocytes. The EUTCD is made up of three directives, the parent directive (2004/23/EC) which describes the broader legislation and two technical directives (2006/17/EC and 2006/86/EC), which detailed the requirements of the EUTCD. Wingfield and Cotell et al. debated the repeated screening (HIV, HBV, HCV) and advocated an initial baseline screening combined with appropriate risk reduction measures to prevent cross-contaminations during an ART procedure.[14] Molecular validation techniques can have a 24hr+ turn-around time, and can be expensive for patients with a minimal income that have limited or no health insurance. The WHO guidelines on HIV rapid testing and counselling services in resource constrained settings stated that rapid tests are inexpensive, simple to perform, single tests, with a shelf-life of approximately 12 months.[15] With such basic screening technology available in South Africa for BBV at affordable costs, all patients should be screened and positive results confirmed with molecular tests. Our preliminary experiences on using rapid tests (HIV, HCV, HBV) as a first-line laboratory test prior to ART are that these tests are easy to perform, and take approximately 20 minutes to acquire results. HIV positive results are confirmed with a secondary more extensive rapid test, and patients are counselled to undergo a confirmatory viral validation test (preferably with CD4 and viral load analysis). The cost for a single HIV rapid test[1] is currently approximately 1.3% of a RT-PCR quantitative (HIV-1 RNA) and 7% of an ELISA HIV-1 test. No false positive or false negative results were encountered for the rapid tests up to date. Eight percent of patients, that have never undergone an HIV-test previously, tested positive with the rapid tests (n = 50 couples).

Four possible combined or separate approaches can be followed when dealing with bacterial contaminants in semen prior to an ART cycle, i.e: (i) provide guidelines on sample collection to male patients to reduce skin-contaminants, (ii) prescribe suitable treatment based on susceptible testing of semen, prior to an assisted reproduction procedure (opposed to prophylactic antibiotic treatment), (iii) semen washing procedures, and (iv) the use of a physical device (e.g. the ProInsert™, [Nidacon, Sweden]) together with discontinuous density gradients to diminish microbe re-contamination in the processed sperm sample.[6] If, by exception a semen/urine sample cannot be submitted for microbial-culture and sensitivity tests, then the option exists to prescribe generic antimicrobials (at a minimal cost), prior to an ART attempt. The macroscopic and microscopic appearances of a semen sample can also be an indicator (e.g. yellow colour and cellular content) of latent infections. The WHO laboratory manual commented that leukocytospermia may indicate the presence of an infection and can be associated with poor sperm quality.[16] Herewith, indicators such as male patients who present with questionable spermiograms, are diagnosed with BBV, or couples who are at risk (accurate anamnesis and physical examinations); can inter alia be used to initiate antimicrobial treatment in the absence of microbiological pathology services.

Sperm preparations

'Semen quality is taken as a surrogate measure of male fecundity in clinical Andrology, male fertility, reproductive toxicology, epidemiology and pregnancy risk assessments'.[17] Semen analyses are usually requested to check the male's possible contribution during the quest for pregnancy and to plan ART procedures (taking into account various sperm parameters such as sperm concentration, motility and morphology), which can be quite costly (see section ART procedures). Therefore to probe the appropriateness of sperm preparation techniques and costs to obtain a purified sperm fraction for

1HIV-1/2 Ag/Ab Combo fourth generation rapid in vitro immunoassay (Determine®) compared to a quantitative HIV-1 RNA reverse transcriptase polymerase chain reaction (RT-PCR, Cobas AmpliPrep-Cobas Taqman HIV-1 version 2), compared to an automated enzyme linked immunosorbent (ELISA, Abbot 4th Generation assay) test

a specific ART procedure, the following should be considered: Which sperm preparation technique is optimal for which ART procedure? Should a semen sample from a HIV-seropositive patient be processed differently from a sample from a HIV-negative male?

Semen characteristics are highly variable, and are not the sole indicator of a couple's fertility, but can be compared to reference values/limits obtained from fertile males (partner's conceived spontaneously within 12 months of unprotected sexual intercourse) during the work-up of a couple.[17] Ombelet et al. is of opinion that if the female presents without a tubal factor and a purified sperm fraction of more than 1 million motile sperm is available from the male partner, then at least three IUI procedures can be performed before moving to an IVF attempt.[7,18] If less than 1 million inseminating motile sperm count is available, the sperm morphology should be ≥ 4% to perform an IVF cycle; however if the sperm morphology is <4%, an ICSI should be performed (sperm morphology according to the Tygerberg criteria).[19] Also if <30%, or no oocytes fertilized during an IVF cycle, the couple should then be counselled for a future ICSI attempt (See Ombelet et al. for a proposed treatment strategy according to the couple's aetiology).[7,18] The quality of sperm yield after sperm preparation, therefore directly influences ART treatment choices. A recent Cochrane review by Boomsma et al. indicated that no specific semen preparation technique (i.e. density gradient centrifugation; swim-up; as well as wash and centrifugation technique) improved clinical outcome with reference to IUI procedures.[20] Ombelet et al. explained that the type of sperm preparation method is secondary to inseminating with a minimum threshold of >1 million harvested spermatozoa for successful conception through IUI.[18]

The choice of a sperm preparation technique is however critical when processing sub-optimal semen samples for IVF or ICSI. Three sperm preparation methods are described in the WHO laboratory manual for the processing of human sperm, i.e. the direct swim-up, and using centrifugation, simple washing technique and discontinuous density gradients.[16] Using the direct swim-up technique, motile spermatozoa can be obtained from semen samples with a low number of motile sperm for IVF/ICSI. Layering sperm culture media over liquefied semen or the latter under the culture media will result in harvesting motile sperm, but at a lower yield in comparison to a washing procedure.[16] Albeit time-consuming, the direct swim-up technique or the capillary-cumulus oophorus model can be used to select motile spermatozoa at minimal costs.[16,21] These techniques are ideal in selected cases or in a low-resource setting since the procedure is inexpensive and requires minimal equipment (no centrifugation involved). The direct swim-up technique is also frequently used for semen samples that are mostly normozoospermic (with reference to sperm number, motility and morphology). A semen preparation kit containing a syringe-like semen processing device called Sep-D (Surelife) is commercially available; whereby the device is pre-filled with a buffered culture media and incorporated with the direct swim-up technique to separate motile spermatozoa from seminal plasma (www.surelifeivf.com). Gentis et al. is of opinion that this office-based semen preparation technique is useful and valuable, since the method is economical (no laboratory facility is needed), resulting in a good clinical outcome for IUI patients in a controlled randomized study.[22] The simple washing procedure entails the dilution of the semen sample with sperm culture media, followed by centrifugation; the resultant sperm pellet is subsequently resuspended in culture media and the centrifugation step repeated. This washing method is most frequently used for the preparation of IUI (and IVF) samples, since the procedure usually delivers a high yield of spermatozoa, if the semen sample is of good quality.[16] Oligozoospermia, teratozoospermia or astenozoospermia semen samples (i.e. sperm numbers, morphology and motility, respectively sub-optimal) should be processed using discontinuous density gradients to optimize samples for IVF/ICSI. These procedures are relatively expensive; require the use of commercially prepared density gradients (silane coated colloidal silica particles) and sperm washing media within a laboratory setting. Based on the cell density and sperm motility, a fraction of highly motile purified spermatozoa is formed at the bottom of the tube during centrifugation.[16] Cell debris and other non-sperm cells (including microbes) are contained within the density gradients, after centrifugation. These layers are then removed via pipetting, and the soft sperm pellet is washed free of the density gradient using a clean tube.[16] Each laboratory should however customize sperm preparation techniques according to the patient's aetiology, i.e. to optimize sperm purification and establish optimal volumes, centrifugation parameters and a combination of the washing and a swim-up technique, or if discontinuous density gradient centrifugation (DGC) with or without washing and a swim-up step should be performed. Sperm preparation techniques can, however, not guarantee a total effectivity to eliminate infectious agents from semen and the risks associated with sperm washing should be discussed with patients.[16,23]

A Cochrane based review by Eke and Oragwu indicated that published data on the use of sperm washing for HIV-seropositive patients are merely observational in nature.[23] 'Sperm washing' refers to a three step procedure, i.e. DGC, washing of the sperm pellet and swim-up step; as was initiated by Semprini and co-workers two decades ago (1992) to prepare semen samples for ART from HIV-positive males, prior to the advent of highly active antiretroviral treatment or the ability to validate absence of viral particles in the washed spermatozoa aliquot.[24,25] No seroconversion in treated patients or in their delivered offspring was reported in the literature, after using purified sperm from HIV-positive patients. This overwhelming safety record is supported by published data from European centres using IUI, IVF and ICSI procedures; and reports from ART centres in the United States where ICSI is predominantly preferred as the ART method of choice for HIV-positive males. HIV-regulations, disparities in ART treatment modalities, as well as costs of sperm washing and ART procedures (with particular reference to resource-limited countries in Africa) may well contribute to the lack of equivalent randomized trials in this area of ART.[23]

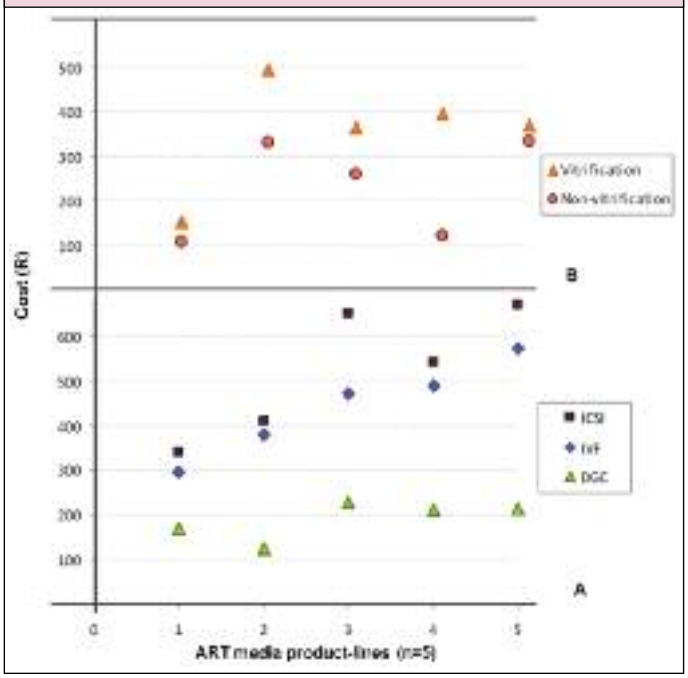
Based on research at our laboratory, the term "sperm decontamination" was coined to distinguish sperm washing from the decontamination procedure used for samples possibly containing various infectious microbes e.g. bacteria, HIV, HCV and CMV.[6] This entails the layering of density gradients and the semen using a ProInsert™ (www.tekevent.com/nidacon/proinsert), and to retrieve the purified motile sperm pellet (after centrifugation) using an elongated pipette without re-contaminating the pellet with infectious micro-organisms. A final washing step follows and a portion of the purified sperm sample is submitted for testing (HIV-1 proviral DNA and RNA using a sensitive molecular based technique such as reverse transcription polymerase chain reaction (RT-PCR)). Neat semen will also be subjected to viral validation during an initial diagnostic semen evaluation visit to the laboratory. The post-processed sperm samples will be submitted for viral validation if the neat semen sample tested positive for DNA or RNA (approximately 43% of cases) currently at a total cost of approximately R2000 for both DNA and RNA RT-PCR tests. It is important to note that only 57% of all neat semen samples (n = 100) from HIV-positive males tested negative for either HIV-1 RNA quantitatively or DNA qualitatively within this sample group. Approximately 13% of patients presented with an undetectable blood viral load, but with a positive seminal plasma viral load (HIV-1 RNA). Semen samples and the purified sperm samples from HIV positive males should therefore, be handled differently from samples from HIV-negative males i.e. from evaluation, processing to cryopreservation of the purified sample in ionomeric resin (CryoBioSystems, CBS™) high security straws. Excess white blood cells in a semen sample from an HIV+ male, may for example indicate an inflammation or secondary sexual transmitted disease, and or viral shedding which may compromise the decontamination procedure. Samples are processed in a contained environment by trained staff, using specific dedicated equipment. Even though viral validations are expensive, it is possible to streamline the decontamination procedure without increasing risks or costs. Although access to the decontamination procedure is unrestricted for most patients, only a certain number of patients can obtain a government subsidy for the procedure. Patients are in general counselled on the process failure rate, HIV-related health screening (CD4+ cell levels) and additional infectious disease tests, general risk-reduction methods, extra costs for viral validations and cryopreservation of semen samples.

Laboratory facilities, supplies and environmental aspects

"The notion that risk can be eliminated by achieving perfection is not tenable. Risk can, however, be reduced by introducing systems which minimize the possibility of human failure".[26] In a mini-exploration of laboratory related factors that can tip the scale between inadequate to adequate and superior ART interventions, the following could be considered: What are the causal human and laboratory associated factors that can impact negatively on ART outcome? How many brands of embryo culture media are available in South Africa and what are the cost implications? Should best-practice quality control frameworks and directives from developed countries be used to guide emerging or existing ART laboratories in developing countries?

ART laboratory equipment, embryo culture media and disposables are on the whole imported from various parts of the world to South Africa. Due to the complexity and variety of ART consumables and equipment, embryo culture media commercially available in South Africa and some ART equipment will be referred to, in this section. The following culture media is available in South Africa: SydneyIVF (K-SICM & KSIBM two-step protocol; Cook® Ireland, www.cookmedical.com), LifeGlobal media (Global® one-step protocol; IVFonline, USA, www.lifeglobal.com), MediCult media (EmbryoAssist™ & BlastAssist™ two-step protocol; Origio, Denmark, www.origio.com), Quinns Advantage® media (Sage® media products two-step protocol; CooperSurgical, USA, www.coopersurgical.com) and Vitrolife AB - G-series™ media (G-1™ & G-2™, two-step protocol; Scandinavia IVF Science, Göteborg, Sweden; www.vitrolife.com). Quotes for the five media brands were obtained from South African agencies responsible for the distribution of the media, in April 2012. The total costs (VAT inclusive) for media usage were thereafter calculated per brand, based on the standard operative procedures at the Reproductive and Endocrine Unit for a full ART cycle including DGC, IVF, ICSI (Figure 3A) and cryopreservation procedures (Figure 3B). The mean cost for DGC solutions used during the processing of a 2ml semen sample, was R190.40 ± R42.80 (R125 min - R230 max). An IVF procedure for 6 oocytes was R441.20 ± R106.70 (R296 min – R573 max) and cost approximately 15% less than an ICSI procedure (mean cost of R521.20 ± R144.70 (R339.00 min – R668.00 max)). Cryopreservation

Figure 3: Costs for ART media product-lines available in South Africa. Cost calculated per patient, per cycle attempt, according to protocol.



solutions using non-vitrification procedures cost an average of R230.00 ± R109.90 (R106.00 min – R332.00 max), with a cost increase of approximately 35% for a vitrification attempt (mean of R354.20 ± R124.80 (R151.00 min – R492.00 max)). These costs purely refer to expenditure with regards to vitrification solutions, excluding the very expensive cryopreservation carriers/devices available as open or closed single-straw systems, cryo-storage tanks, or liquid nitrogen. Good quality supernumerary embryos should always be cryopreserved for future use. Cost-effective prevention of ART-related multiple pregnancies (and associated risks) is highly recommended, especially in a developing country, whereby the embryos or blastocysts should be cryopreserved/vitrified preferably in single carriers/devices for thawing.[8] Recent South African legislation indicated that: ''No more than three zygotes or embryos may be transferred to the recipient during an embryo transfer procedure, unless there is a specific medical indication to the contrary'' (For more information see www.fertilitysa.org.za/deptofhealth/index.asp). South African ART providers are however, already following the European drive of elective single embryo transfer or the ESHRE revised guidelines for good practice in IVF laboratories, which stipulates that not more than two embryos should be, transferred.[27]

Embryo culture media has evolved over the past thirty years and can be grouped into a ''let-the-embryo-choose'' principle, a one-step or monoculture system and the ''back-to-nature'' principle or a two-step sequential embryo culture system.[28,29] Above and beyond the quality and renowned international reputation of ART media product lines, the selection of the product line will be influenced by the following: affordability of the range; order and delivery dates; the response rate and knowledge of the company representative on the ART products, and ability to deliver items timeously, with back-up media available if needed; optimal courier and transport conditions guaranteed from the manufacturing site to the client; shelf-life and, ease of use of the products.

A retrospective cost analysis in 1986 for the set-up of our ART unit (then called the Reproductive Biology Research Unit), by Fourie and co-workers, indicated that equipment cost a total of R138,000. A single inverted microscope, two water jacketed upright incubators, a stereo as well as a light microscope, a laminar flow and biological safety cabinet, hygrometer, dry-oven, centrifuge, refrigerator, osmometer, pH-meter and electronic balance constituted the laboratory to initiate the ART programme.[4] Some of this original equipment was made redundant in 2005/6 when the laboratory moved to new purpose built laboratories within Steve Biko Academic Hospital. Quotes obtained on comparable high quality equipment in May-July 2012, indicated that similar type and number of equipment will have a price tag between R800,000 and R1.1 million depending on the model size and/or brand type. It is interesting to note that the latter mentioned historical article does not mention a micro-manipulator (for ICSI procedures), or any cryopreservation equipment during the initiation phase of the laboratory. Mouth pipetting of zygotes and embryos as well as in-house culture media preparation was permitted in the eighties. ART equipment at the present time focuses on imaging, modular equipment such as benchtop incubators with accent on temperature and gas control during the ART procedure.

In most instances are offices, rooms, wards or theatres customized and adapted to function as ART laboratories in developing countries, whereby air quality and humidity are the most difficult factors to regulate.[6] Many assisted reproduction laboratories in South Africa had very humble beginnings in the mid-eighties/nineties and have grown into formidable internationally recognized laboratories over time. Ombelet et al. is of opinion that ART procedures and screening can be simplified and alternative culture methods should be investigated to perform ART in a low-cost environment.[8] Therefore, ART techniques are feasible if embryo culture conditions can be quality controlled and maintained (aseptic milieu, with optimal temperature, pH and gas control) within a less than perfect outer infrastructure. Basic administrative and infrastructural changes can, however, improve laboratories at a minimal cost, e.g. having clutter free work surfaces, strict access control (to prevent unauthorised staff visits during a procedure and to ensure safety), as part of a detailed quality control program, removal of basins to prevent contamination with water-borne pathogens, hazardous waste containment, maintaining a relative warm (>25°C) laboratory room temperature within a dust free environment, and refrain from using any volatiles (solutions or products) within the embryology laboratory. The revised guidelines by the European Society of Human Reproduction and Embryology described in detail how to ''promote assurance of good laboratory practice and to define the concept of a qualified embryologist''.[27] ART policies and procedures are outlined in the publication; together with particulars on laboratory staffing and safety (including laboratory design, equipment, infectious agents, and protective measures); laboratory procedures (from patient identification, preparation and execution of procedures, to traceability of steps of the procedure), as well as quality control and quality assurance. The majority of the first-world ART guidelines will add value to South African ART practices, and are probably already applied, with the likely exception of smaller office-based ART providers. These guidelines can be adapted into safe and workable directives to protect patients and health workers in developing countries, but within the framework of national regulatory bodies that represents all ART providers. Being in-step with international guidelines/directives will also steer ART providers towards best practices in the absence of national directives/guidelines on specific ART procedures.

Conclusions

Childlessness is a condition whereby a couple can not contribute to the future of a community within a social structure where children signify security and continuance of life. The demand for ART in South Africa is not in doubt, the path leading to and access to ART procedures, is however uncertain. ART laboratory equipment, tests, culture media, and disposables can contribute between 30-

50% of ART costs in the private ART sector. The value and relevancy of diagnostic tests and screening policies, preparation techniques, choice of media, devices and equipment should however, not be underestimated, and can differentiate between inadequate to adequate and superior ART interventions. The ultimate goal of ART should be to achieve a healthy singleton as cost effectively as possible, especially in a developing country, making use of valid techniques and equipment, without compromising treatment virtue.

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