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Global access to infertility care: The Walking Egg project

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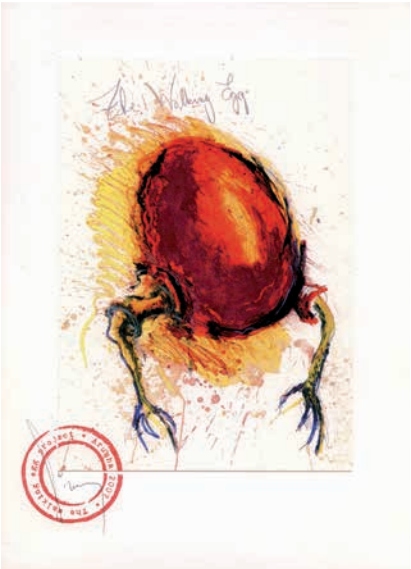

The Walking Egg is a non-profit organization (npo) founded in 2010 to realize the Arusha Project which strives to implement accessible infertility programs in resource-poor countries. The project aims to raise awareness surrounding the childlessness and to make infertility care in all its aspects, including assisted reproductive technologies, available and accessible for a much larger part of the world population.

All scientists involved have agreed to donate the royalties of all inventions made in the frame of this project to the npo, also the founding member and well known artist Koen Vanmechelen contributes actively to the fundraising of this global project. He has made a beautiful litho, now covering this monograph, which will be sold at an affordable price – the calculated price of one low-cost IVF cycle in developing countries – to everyone who wants to support reproductive health care in resource poor countries.

More info can be found on the websites www.thewalkingegg.com

The most beautiful thing we can experience is the mysterious.
It is the source of all true art and all science. (Albert Einstein)

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Editorial

The Walking Egg visits South Africa

Infertility care is one of the most neglected health care issues in developing countries, affecting more than 200 million couples. The social stigma of childlessness still leads to isolation and abandonment. Bilateral tubal occlusion due to sexually transmitted diseases and pregnancy-related infections is the most common cause of infertility. Consequently most cases of infertility are only treatable by using assisted reproductive technologies (IVF, ICSI) which are either unavailable or too costly.

December 2007 an expert meeting was organized in Arusha, Tanzania by the Walking Egg non-profit organization in cooperation with ESHRE. This meeting was the start of a global project aiming at increasing the diagnostic and therapeutic options for childless couples in resource-poor countries. To optimise infertility care in terms of availability, affordability and effectiveness, our main objectives are (1) the establishment of a low-cost "one-stop clinic" for the diagnosis of infertility, (2) the simplification of IVF procedures and (3) the implementation of "accessible" infertility services, integrated within health care clinics dealing with good quality family planning, health education, maternity- and child care facilities.

We recently developed a simplified IVF laboratory culture system in which excellent culture conditions are reproducibly obtained without the need for medical gases, complex incubation equipment and expensive infrastructure. An embryo implantation rate of 35% was reported which to date has resulted in eighteen healthy babies.

Time has come to start with accessible and affordable infertility centres worldwide. Lowering the cost of the diagnostic phase, using mild and less expensive ovarian stimulation protocols in combination with the simplified IVF procedure will make it possible to reduce the costs for IVF by almost 80%.

But it remains important to go on with clinical research on different aspects of the low-cost IVF strategy: which ovarian stimulation protocol(s) are to be used, how many motile spermatozoa do we need to be successful with this method, prevalence studies on infertility in developing countries, socio-cultural follow-up of the different projects etc.

Therefore we decided to organize a meeting in South-Africa, bringing together the main actors in this project and representatives of the interested centres and patient groups in Africa.

The final objective of the Walking Egg Project is the implementation of infertility services in many developing countries preferably integrated in existing family planning and mother care services. We hope that this meeting will encourage people to go on with this very controversial but much needed project.

Willem Ombelet
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Global access to infertility care: The Walking Egg Project

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Abstract

The consequences of involuntary childlessness in developing countries (DC) create more wide-ranging societal problems compared to Western societies, particularly for women. Negative psychosocial and economical consequences for childless couples are often severe and underestimated by the local and international society.
In the Walking Egg Project we strive to raise awareness surrounding childlessness in resource-poor countries and to make infertility care in all its aspects, including assisted reproductive technologies, available and accessible for a much larger part of the world population.
As part of the project we recently developed a simplified 'WE lab IVF culture system with excellent results (see paper of Klerkx et al.).
We also realize that universal access to infertility care can only be achieved when good quality but affordable infertility care is linked to effective family planning and safe motherhood programmes. Only a global project with respect to socio-cultural, ethical, economical and political differences can be successful.

Key words: **Assisted reproduction, developing countries, infertility care, IVF, resource-poor countries, sociocultural factors.**

Introduction

Infertility is a global reproductive health problem: a silent population of more than 180 million couples worldwide is facing the consequences of childlessness day by day (Rutstein & Iqbal, 2004; Boivin et al., 2007).

Consequences of infertility are numerous: stress, depression, low-self esteem, guilt, marital problems, and sexual problems. This may result in physical and psychological violence and polygamy (Daar and Merali 2002, Dyer 2004 2005; Ombelet et al. 2008). In the last two decades the manifold consequences of infertility, most significant within DC, at personal, conjugal, family and community levels, and financially, are well documented (Inhorn, 2003; Van Balen and Bos, 2009). These studies have also shown that the way people experience, explain and deal with infertility is strongly related with their socio-cultural and economic life circumstances as well with the availability or non-availability of health care options.

The most important reasons for infertility in DC are (1) the high incidence of sexually transmitted diseases (STDs) – which affects both men and women – and (2) pregnancy-related infections, due to unsafe abortions and home deliveries in unhygienic circumstances, mainly in rural areas.

Despite the severe economical consequences of childlessness in DC, infertility care remains a low priority area for local health care providers (Fathalla et al., 2006; Ombelet, 2011).

The Walking Egg non-profit organization

The Walking Egg npo has opted for a multi-disciplinary and global approach towards the problem of infertility (Dhont, 2011). The main goal of the Walking Egg Project is to raise global awareness surrounding childlessness, and to make infertility care in all its aspects universally available and accessible. Therefore we need to change and optimise the whole set-up of infertility care in terms

of availability, affordability and effectiveness (Ombelet and Campo, 2007).

To realize our objective we have (1) to raise awareness surrounding the problem of childlessness within (a) the donor community, politicians, funding agencies and research organisations through lobbying and publishing, (b) the general population through information, education and counselling on infertility and its consequences, (2) to study the ethical, socio-cultural and economical aspects surrounding the issue of childlessness and infertility care in resource-poor countries, (3) to develop new methods to make infertility diagnosis and infertility treatment including ART accessible for a much larger part of the population, by (a) simplifying the diagnostic procedures and (b) simplifying the IVF laboratory procedures and (c) modifying the ovarian stimulation protocols for IVF and (4) to work together with other organisations and societies working in the field of reproductive health.

Simplified infertility treatment and non-IVF assisted reproduction

If tubal patency is demonstrated in ovulatory women and if severe male factor subfertility has been excluded, fertility awareness programmes are an inexpensive and efficient first line approach to infertility management (Gnoth et al., 2002, 2003). Fertility awareness counselling to couples about the meaning and detection of cervical mucus secretion can be given by nurses and paramedical staff working in existing reproductive health care centres.

For ovulatory dysfunction, representing almost 20% of female infertility, clomiphene citrate (CC) is a very cheap and rewarding option. In case of resistance to CC, a low dose ovarian stimulation regimen with gonadotrophins aimed at mono-follicular growth is advisable, although this medication is more expensive.

In case of unexplained and moderate male factor infertility and provided tubal patency has been documented, intrauterine insemination (IUI) with husband's semen in natural cycles or after mild stimulation is an excellent first-line treatment without major costs and without expensive infrastructure (Ombelet et al., 2003;2014; Verhulst et al., 2006). IUI programmes can be runned by well-trained paramedical staff, another advantage for developing countries.

Simplified IVF laboratory procedures

Another major challenge is to reduce costs of laboratory procedures, namely fertilization and culture of eggs and embryos for IVF. Different options and approaches have been developed or are presently being field- tested with promising results. As part of the Walking Egg Project and based on previous findings and experience (Van Blerkom and Manes, 1974; Swain, 2011) we developed a new simplified method of IVF culturing, called the 'WE lab method (see Klerkx et al. paper). With this new system, specifically designed for low resource settings, we can avoid the high costs of medical gases, complex incubation equipment and infra-structure typical of IVF laboratories in high resource settings.

Low-cost ovarian stimulation protocols for IVF

Effective, cheap and safe stimulation schemes for intrauterine insemination (IUI) and IVF need to be established. A review of the literature clearly shows the value and effectiveness of mild ovarian stimulation protocols in ART settings. The use of clomiphene citrate (CC), a very cheap oral drug, has been proven in many studies to be an optimal alternative with acceptable results, minimal side effects and a very low complication rate (Ingerslev et al. 2001; Nargund et al. 2007; Verberg et al. 2009; Kato et al. 2012).

The implementation of 'WE pilot-centres in DC

The ultimate goal of the Walking Egg npo is the implementation of good quality but low-cost infertility centres in DC, if possible and preferable integrated into existing reproductive health care programmes.

The selection of countries where the first pilot centres are implemented will be based on (1) available data on the resources, needs and resource gaps for infertility services on a national level, (2) the availability of endoscopic surgery facilities in the neighbourhood, (3) a good quality family planning unit, (4) good quality mother care facilities and (5) the availability of at least one experienced and dedicated gynaecologist and biologist.

Conclusion

The magnitude of childlessness in developing countries has dimensions beyond its prevalence. Although reproductive health education and prevention of infertility are number one priorities, the need for accessible diagnostic procedures and new reproductive technologies is very high. The success and sustainability of ART in resource-poor settings will depend to a large extend on our ability to optimise these techniques in terms of availability,

affordability and effectiveness. By simplifying the diagnostic and IVF laboratory procedures and by modifying the ovarian stimulation protocols for IVF assisted reproductive techniques can be offered at affordable prices.

We believe that infertility care will be one of the more predominant components of future reproductive health care practice in developing countries.

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A Simplified IVF Laboratory Method

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Introduction

Reproductive care as a universal right has been neglected for a long time. Whilst conventional countries developed state of the art equipment to perform assisted reproductive technologies (ART) with high success rates, developing countries or so-called 'resource-poor countries' were left in the dark (Boivin et al., 2007; Cates et al., 1985; Rutstein and Iqbal, 2004). Estimates on worldwide infertility prevalence show that between 52.6 to 72.4 million couples are affected by the lack of medical assistance in resource-poor countries to achieve a pregnancy (Mascarenhas et al., 2012). The prevalence of infertility is directly related to the high number of sexually transmitted diseases and pregnancy-related infections in developing countries (Ombelet et al., 2008). Consequently, most cases are only treatable by using IVF/ICSI treatments, which are too costly or unavailable in large parts of the world. If infertility is not caused by a severe male factor, conventional IVF treatment can be sufficient. However, fertilizing and culturing embryos in an IVF program can represent over 50% of the total financial cost (Aleyamma et al., 2011). Some attempts have been made to develop a system to perform an IVF treatment without a large investment in a laboratory installation. As part of the Walking Egg Project (Dhont, 2011; Ombelet, 2013; 2014) and based on previous findings and experience (Van Blerkom and Manes, 1974; Swain, 2011) we developed an IVF methodology that is simple, safe and effective in treating infertile patients in a low-resource setting without loss of success rates compared to a conventional IVF environment. We estimate the cost of the simplified laboratory method, which we named tWE-lab IVF culture system, between 10-15% of the current cost in a high-resource setting. Regular IVF programs are not suitable for couples with moderate or severe male factor because the number of spermatozoa for insemination is too low. In the tWE-lab IVF culture system, only 1000-5000 good motile spermatozoa are needed to achieve good fertilization results, making it suitable for a large part of the patients requiring IVF/ICSI, including those with moderate male factor (Van Blerkom et al., 2014).

The tWE-lab system is based on a simple chemical reaction in a closed environment which removes the need for an expensive IVF laboratory with CO_2 incubators, medical gas supply and air purification systems. CO_2 is necessary to equilibrate the pH of the IVF culture medium to a value between 7.25-7.40, optimal for embryo development. Continuous culture at 37 degrees Celsius is necessary for viability of the embryo and can be achieved by an incubator, heated box or warm water bath. The simplified IVF method uses 2 chemicals, citric acid and sodium bicarbonate, to produce the CO_2 necessary to adjust the pH. The use of these chemicals for pH equilibration in a closed environment had been described (Swain, 2011) and Van Blerkom used the idea to transport animal oocytes already 30 years ago (Van Blerkom and Manes, 1974). The tWE-lab system was designed in collaboration with Dr. Van Blerkom and is now a standardized procedure to perform an IVF treatment, for which all materials are available in a compact ready-to-use kit.

The simplified IVF method uses 2 glass tubes in which the first tube serves as the generator of CO_2 by a chemical reaction between citric acid and sodium bicarbonate to produce the CO_2 for equilibration of the culture medium in the second tube (Fig. 1). A connection between the tubes is established by needles and tubing to transport the produced gas from the generator tube to the tube with culture medium. The connection can easily be

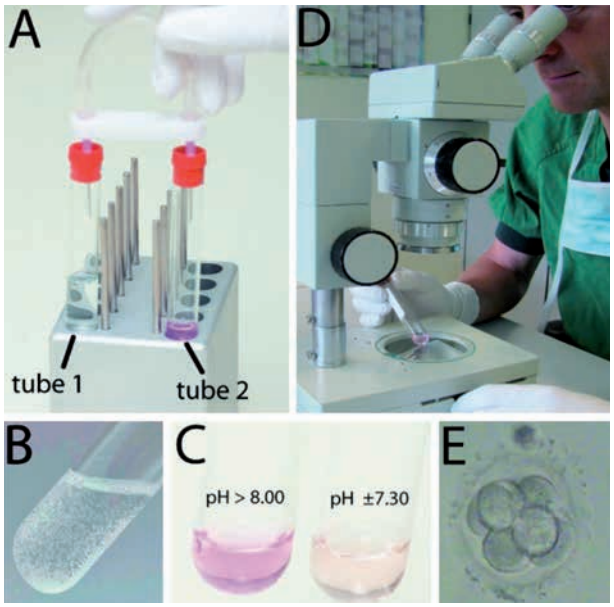

Fig. 1. — tWE-lab method: (A) Equilibration of the culture medium in tube 2 by the CO_2 produced in tube 1, (B) production of CO_2 in the generator tube, (C) phenol red shift from dark pink (pH>8.00) to salmon pink (pH around 7.30), (D) embryo evaluation through the glass walls of the closed tubes, (E) an embryo visualized in the tWE-lab tube.

removed after the 24-hour equilibration of the culture medium has completed. The tubes with culture medium can be used immediately or they can be stored in a cold (2-8 degrees Celsius) environment. To keep warm, the tubes are placed in a heated block (alternatively water bath or simple incubator without the need for a gas supply) at 37 degrees Celsius. After oocytes have been harvested from the follicles, they are inserted individually in the equilibrated tubes using a 1 ml syringe and needle, without opening the tube or disturbing the air environment inside the tube. The tWE lab system provides a closed environment to ensure stable culture conditions and protect the gametes and embryos from possible adverse external effects. Between 1000 and 5000 washed sperm cells are injected in a similar way to the tubes to inseminate the oocytes. After 24 hours, fertilization is assessed by keeping the tubes at a slant and looking through the glass walls at the oocytes to see the 2 pronuclei that are a sign of sperm protrusion. Fertilization and embryo development are assessed through the glass walls of the tube. This simplified method removes the need for expensive air control systems and gives a very stable and safe environment for embryos to develop. The search for the materials needed in the kit has been extensive and all items have important specifications that ensure good operation of the low-cost IVF method. Changing as little as the tube or the needle can result in a complete loss of function of the tWE-lab system as all components are strictly chosen to match each other.

Outcomes from the low-cost culture method were compared with those from a conventional IVF culture system in a study conducted at the IVF unit in Genk Belgium and were shown to be identical (Van Blerkom et al., 2014). As the study was performed in routine IVF cycles, surplus tWE-lab embryos were frozen and embryos that originated from the tWE-lab system that were thawed and transferred have also led to the birth of healthy children (Ombelet et al., 2014). These studies prove the tWE-lab system to be an alternative low-cost system for a routine IVF procedure. Next step is to implement the tWE-lab IVF system in a centre that is limited in resources. Our goal is to open the first low-cost tWE-lab centre in Ghana in 2015. Preparations for the set-up of the centre are ongoing. If our method can be reproduced in other centres we believe this will reach a large part of the worlds' infertile population and finally provide equity and social justice for many childless couples currently still left without resources and help (Ombelet, 2011).

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Implementation of hysteroscopy in an infertility clinic: The one-stop uterine diagnosis and treatment

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Prevention of multiple pregnancies after assisted reproduction: the Belgian project

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Abstract

An increased incidence of maternal, perinatal and childhood morbidity and mortality has been described due to the epidemic of iatrogenic multiple births as a result of infertility treatment. The result is a much higher healthcare cost of infertility therapy which automatically will lead to social and political concern.
Single embryo transfer in selected cases seems to be the best option in reducing the number of multiples after IVF/ICSI. The Belgian project in which reimbursement of ART-related laboratory activities is linked to a transfer policy aiming at substantial multiple pregnancy reduction and taking into account the age and cycle number of the patient, is a good example of forward-looking health economics. The twin pregnancy rate has dropped to 10% and triplet pregnancies almost disappeared.
Considering non-IVF assisted reproductive technologies: a low multiple pregnancy rate of less than 5% is noted in Belgium for IUI procedures with homologous and donor semen. This can easily be explained: in almost 80% of IUI cycles no ovarian stimulation (natural cycle) or clomiphene citrate has been used. When gonadotrophines are used, our aim is to support the growth of one or two follicles, so avoiding the high risk for multiples.

Key words: **Cost-effectiveness, IUI, infertility treatment, IVF, multiple pregnancies, policy, reimbursement.**

Introduction

The major side effect of assisted reproductive technology is undoubtedly the high incidence of multiple pregnancies, responsible for a substantial part of the costs and suffering. By the end of the 90s assisted reproduction (ART) accounted for 0.08-0.16% of the total health care costs in the Nordic countries (Granberg et al., 1998) while in the USA expenses for infertility, including IVF, were responsible for 0.4-0.8% of these costs (Stovall et al., 1999; Griffin and Panak, 1998).

In terms of absolute figures and because of their higher incidence, twin pregnancies outweigh by far the effect of high-order multiple pregnancies. The most efficient way to reduce the costs and the distress experienced by couples in ART is the prevention of multiple pregnancies, not only the high-order multiples, but even more important the reduction of twin pregnancies. For IVF-ICSI the improving insights in embryo quality assessments, followed by single embryo transfer could be the method of choice, especially in the good prognosis group.

Avoiding multiple pregnancies: why?

In most developing countries, 30% to 50% of all twin pregnancies are linked to infertility treatment. In 2000 and 2001 the perinatal mortality (PNM) of singletons in Flanders was 6.7 per 1000 births, in twins the mortality rate rose to 26.9 per 1000 births, while higher order multiples even reached PNM rates as high as 68.2 per 1000 deliveries (Cammu et al., 2002). Preterm delivery occurs in more than 80% of triplet and 100% in quadruplet pregnancies. Very low birth weight infants are derived 9 times and 29 times more often in twin and triplet pregnancies respectively. This leads to an increased rate of neonatal care admission, more days of ventilatory support and a higher frequency of intraventricular haemorrhage and necrotizing

enterocolitis. Long-term infant morbidity is reflected in mental and physical disabilities. At least one handicapped child is found in 7.4%, 21.6% and 50% for twin, triplet and quadruplet pregnancies respectively.

Maternal complications include a significant increase in anaemia, gestational diabetes (10%), hypertension, pre-eclampsia (30%) and post-partum haemorrhage (10%). Dystocia and a high caesarean section-rate will contribute to the excess maternal morbidity. All these complications lead to a dramatic rise in days of hospitalization and the subsequent increased financial costs.

On the other hand, pressure to achieve higher pregnancy rates in infertility treatment have resulted in an unacceptable high multiple pregnancy rate in many countries. In the United States, multiple births occur after more than 35% of IVF cycles (Katz et al., 2002; Sunderam et al., 2013).

Interesting but most frightening was the observation that, in 1998, of all infants born after IVF and/or ICSI only 57.3% were born as singletons. 37.1% were born as twins and 5.6% as triplets or quadruplet.

Looking at these data, the prevention of multiple gestations became the most important challenge, not only to reduce the economic costs of infertility-related services but even more important to improve perinatal health.

The Belgian project

For IVF/ICSI

In Belgium there has been a steady decline in the number of embryos transferred since 1997. The proportion of deliveries of multiples after ART has also decreased from 34% in 1992 to 24% in 2000. The introduction of single embryo transfer (SET) (Gerris et al., 1999; De Sutter et al., 2002) has certainly accelerated this evolution. SET was performed in 14% of all transfers in Belgium in 2001 and this figure was increasing each year. Surprisingly, this strategy did not affect the overall national results. The ongoing pregnancy rate per transfer has always fluctuated around 20% for the last ten years and remained 22% in 2001, although less embryos were transferred.

Until 2002, about 75% of the medical costs of assisted reproductive technologies were reimbursed by the government. These costs included the medication used, the visits and the costs for monitoring (ultrasonography, hormonal). There was no reimbursement for the laboratory costs at all, neither for IVF-ICSI or IUI.

In 2001 the Belgian government decided to change the reimbursement policy in IVF-related procedures. The first objective was to increase accessibility to infertility treatment. It was mentioned from the start that financial resources were limited and as a result, a certain inventiveness was called for.

Therefore, the Belgian College of Reproductive Medicine (BCRM), in cooperation with all licensed IVF centres, agreed on a proposal to the government in which reimbursement of IVF and ICSI treatment cycles would be linked to a 50% reduction of twin pregnancies, subsequently minimizing the risks for high order multiple pregnancies to almost zero. This proposal was based on a reduction of embryos transferred after ART, considering the possible influence of female age and cycle number on the incidence of multiple pregnancies (Table I). Following a study of the direct laboratory costs for IVF +/- ICSI, it was concluded that 1.250 Euro would be a fair reimbursement for the laboratory

Table I. — Reducing the multiple pregnancy rate in IVF-related procedures using fresh embryos: the Belgian strategy.

Women ≤ 35 years old		
1st attempt	⇒	single embryo transfer (SET)
2nd attempt	⇒	single embryo transfer (SET) if one or more top-embryos are available
	⇒	transfer of two embryos if no top embryo is available
3rd – 6th attempt:	⇒	maximum two embryos transferred
Women > 35 and ≤ 39 years old		
1st and 2nd attempt	⇒	maximum two embryos transferred
3rd – 6th attempt:	⇒	maximum three embryos transferred
Women > 39 and ≤ 42 years old		
1st – 6th attempt	⇒	no limit for number of embryos transferred
Women > 42 years old	⇒	no reimbursement

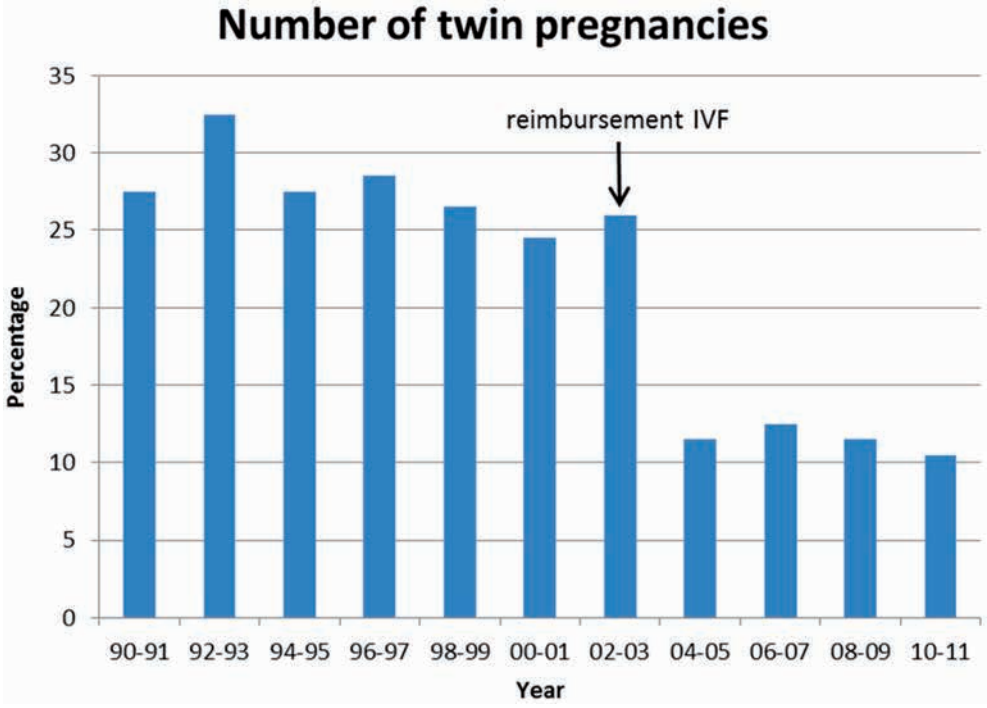

Fig. 1. — Effect of the Belgian reimbursement policy on the number of twin pregnancies.

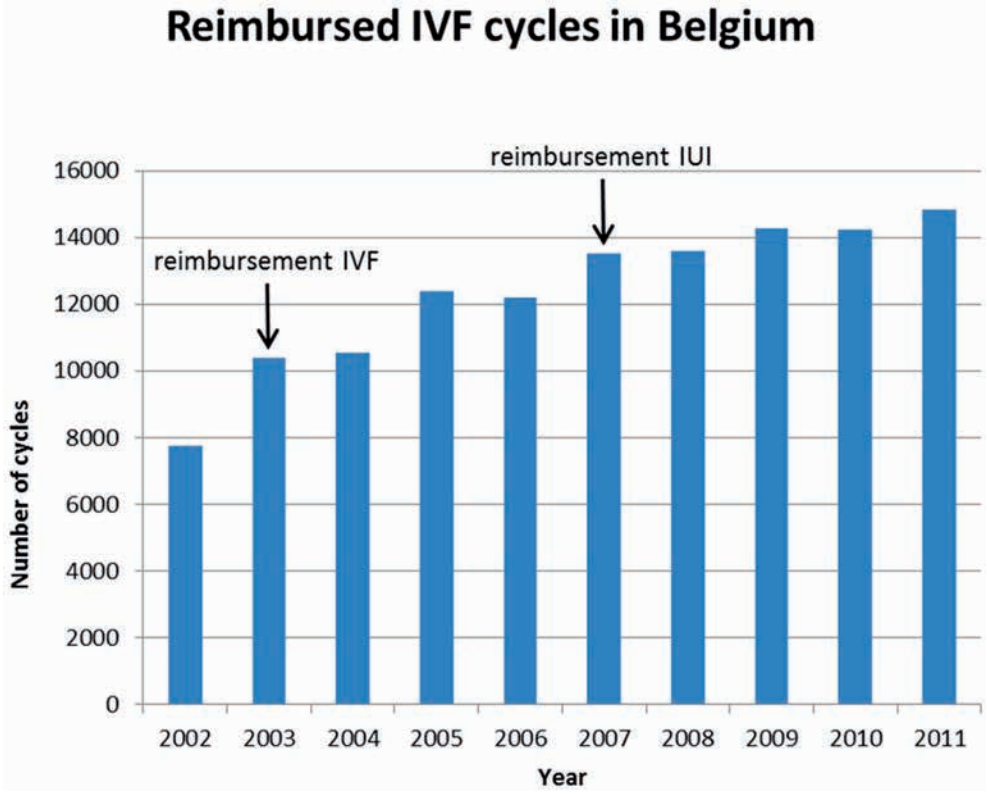

Fig. 2. — Influence of the Belgian reimbursement policy on the number of IVF/ICSI cycles.

costs associated to IVF/ICSI at that moment. The government decided to reimburse 6 IVF/ICSI cycles in a lifetime, provided the suggested strategy dropped from 26.5% in 2002 and 10.5% in 2011 (Ombelet et al., 2005, Fig. 1).

For IUI

It was to be expected that the number of IVF cycles would increase due to the reimbursement policy. The reimbursed IVF cycles almost doubled from

Table II. — Live birth rate (LBR) and multiple pregnancy rate in Belgium (BELRAP data) and Europe (ESHRE data). (AID = artificial insemination with donor semen, AIH = artificial insemination with partner's semen).

	Number of cycles	LBR/cycle	Twin	Triplet
BELRAP 2010-2011				
KID	11031	8,60%		
AIH	19463	6,80%		
Total	30494	7,50%	3,30%	0,01%
ESHRE 2010				
KID	38124	13,80%	7,90%	0,20%
AIH	176512	8,90%	9,30%	0,50%
Total	214636	9,30%	8,90%	0,40%

7759 in 2002 to 14833 in 2011 (Fig. 2). Therefore, the government decided to reimburse IUI treatment as well, in order to avoid too many unnecessary IVF procedures. Due to the fact that in Belgium more than 80% of IUI cycles are performed in a natural cycle or after the use of clomiphene citrate, the live birth rate per IUI attempt but is low compared to other European countries, the advantage is that the twin pregnancy rate is also extremely low, namely 3.3% twins and 0.1% triplets compared to 9.3% twins and 0.5% triplets in 2010 in Europe (BELRAP rapport 2010-2011, Kupka et al., 2014; Table II).

Conclusion

The reduction of embryos transferred after IVF and/or ICSI resulted in a higher proportion of singletons. The Belgian project in which reimbursement of laboratory activities is linked to a limited number of embryos transferred in order to reduce the twin pregnancy rate by 50% and the high order multiplets to almost zero is also unique from a health-economical point of view.

The IUI multiple pregnancy rate in Belgium remains very low due to the use of natural cycle IUI or mild ovarian stimulation protocols with clomiphene citrate and/or low-dose urinary gonadotrophins or recombinant FSH.

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The socioeconomic impact of infertility on women in developing countries

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The World Health Organization (WHO) has classified infertility as a disease affecting approximately 15% of reproductive-aged couples. It is a disease that is not characterized by mortality but rather by the morbidity it inflicts on the individual and the couple. This morbidity includes social, economic, relationship and psychological aspects but is not confined to these. Women especially may be caught in a spiral of attempts to achieve their one social and evolutionary need namely to have a child.

A number of international decisions have placed infertility care in the context of reproductive health as a health priority. For many affected couples improvement or restoration of infertility-related reproductive health requires Assisted Reproductive Technology (ART). Although according to latest reports more than 1.6 million ART cycles were undertaken in 2008 (Chambers et al., 2013). The availability and accessibility of ART differs greatly between regions and countries. An important factor influencing accessibility is the cost of treatment and how these costs are covered. In many countries and especially in low resource settings, ART requires out-of-pocket payments by the consumer and while these may be affordable to some they may be impoverishingly expensive to others. The latter raises the question why couples would be willing to pay for treatment that they are unable to afford.

Studies from Africa and Asia have highlighted the many important roles of children which collectively allow their parents, especially their mothers, to become more esteemed members of the family and community (Dyer and Patel, 2012). Children are a reliable source of manpower in many rural and developing areas (Feldman-Savelsberg, 1994; Gerrits, 1997; Hollos, 2003; Barden O' Fallen, 2005; Hollos et al., 2009) and provide economic security in old age; infertility often leads to instability in a marriage and the possibility of divorce or abandonment with consequent loss of financial security. Certain customary laws and cultural traditions lead to negative attitudes to infertile women and may potentiate the scourge of gender inequality.

Infertility may lead to abandonment and more economic hardship if women have to payback their bride wealth or pay bride wealth for husbands to enter into new unions (Nahar, 2012; Nahar et al., 2011). These social inequalities are reinforced when infertile women are treated as social servants by tending to the sick and infirm (Okonofua et al., 1997; Ruganga et al., 2001) or caring for the children of others (Okonofua et al., 1997; Dhont et al., 2011). Women may not be allowed to inherit or continue living in their husbands compound after he dies (Hollos, 2003; Hollos et al., 2009). Sons are seen to strengthen the lineage and the inheriting capacity of a family (Hollos, 2003) – consequently girl-children are seen as less important thereby reinforcing gender inequality.

The socioeconomic consequences of infertility are not easily overcome by availability to care. Cost of ART is an indicator of the underlying costliness of the countries health system. Consequently, it differs between countries, as does the out-of-pocket payment per individual couple. The cost to consumer is a function of the underlying cost of treatment, the level of subsidization or third party cost coverage and the available income of the consumer.

A study conducted in South Africa identified the extent of out-of-pocket-payment and financial coping mechanisms in couples accessing ART at a public, tertiary referral hospital where ART was subsidized but couples had to pay part of the expenditure (Dyer et al., 2013). Participants were divided into tertiles of socioeconomic status based on annual household per capita expenditure.

Catastrophic expenditure was defined as an out-of-pocket payment greater than 40% of the annual non-food household expenditure. According to results, 20% of couples incurred catastrophic expenditure – 51% of couples were in the lowest socioeconomic tertile. Financial coping strategies included reduced expenditure on food and clothing, use of savings and borrowing money that incurred interest. Half the couples had to take on extra work to offset the cost of ART.

Not only does the cost and funding models of treatment provide an important explanation to the differences in the utilization of available treatment, but they also help to explain clinical practices especially relating to embryo transfer.

Some countries like Israel and Australia have state funded programmes which enable certain state-imposed restrictions to be placed on these cycles. Examples of these include age limits and the requirement for single embryo transfer thereby decreasing the downstream indirect cost of multiple pregnancies and prematurity associated with this (Chambers et al., 2013).

However, developing countries do not have an authority to standardize cost. This leaves women vulnerable to exploitation by both western and traditional medical practitioners (Sundby, 1997, Okonofua et al., 1997). Efforts to make ART affordable in developing countries have been undertaken by non-profit organizations such as the Walking Egg and the Low-Cost IVF Foundation.

Methods to reduce cost of ART exist and must be pursued wherever possible. Introduction of third party funding usually requires the imposition of some restrictions or regulations. Restrictions may apply as to who is given access to ART while regulations may apply regarding number of embryos transferred with the view if reducing the biggest risk of ART, and its resultant downstream costs, namely that of multiple pregnancies. Additional cost reducing strategies include less aggressive stimulation cycles with less monitoring, novel use of incubation techniques, earlier embryo transfers and effective use of cryopreservation. There should be specific start and end points to treatment modalities with age-appropriate and cause-appropriate interventions. Clinics may offer risk sharing, package pricing for multiple cycles or cross subsidization.

Although it is assumed that lower cost of treatment will improve access, this is not always the case. Some studies have indicated that lower socioeconomic and certain ethnic groups may still be disadvantaged (Chambers, 2013). Care must also be taken that more affordable treatment does not lead to inappropriate perpetuation of ART in some couples are caught in an unrelenting pursuit for a child.

The benefits of ART are difficult to quantify but important. They centre on quality of life and happiness. The majority of people consider parenthood as part of the fulfilment of life goals. Cost utility analysis is the main method governments use to guide allocations of public resources to specific health outcomes. This is usually measured in quality adjusted life years (QALY's), which captures improvement in health among living patients. It is very difficult to quantify this for fertility treatment as the creation of new life cannot be captured in the indicator. However, United Kingdom National Institute of Clinical Excellence fertility guidelines incorporated QALY's and concluded that under most clinically appropriate circumstances access to ART treatment and single embryo transfer represented good value for money from a societal perspective (www.guidanceniceorg.uk).

Improving access to infertility care requires a two-faceted approach. Infertile couples must be able to access quality care at affordable cost, however this is attained. In addition, efforts to prevent infertility should be escalated – according to the WHO up to 45% of adult conditions develop during adolescence and this is the target group for education regarding preventative strategies.

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Need for accessible infertility care in Ghana: the patients' voice

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Introduction

The list of Reproductive health care services as contained in the Programme of Action of the International Conference on Population and Development (ICPD) held in Cairo, Egypt, in September 1994 includes the "prevention and appropriate treatment of infertility". Unfortunately, this is an area that has been overlooked so far. While the health insurance systems of most developed nations take care of ARTs treatments and in some instances people going through the treatment receive refunds for as much as six cycles, their colleagues in developing countries including Ghana are left to their fate. It is very disheartening that infertility and people living with infertility in developing nations particularly Africa, do not have the needed support. Africa is said to be poor, overpopulated, with high fertility rates etc. Consequently it is difficult to get funding/support for infertility activities even though people living with infertility in Africa are the worse hit among infertility patients worldwide.

Infertility in Ghana

The traditional Ghanaian society is pro-natal, where the ultimate purpose of marriage is to produce children who will continue the name of the family (Gyekye, 1996; Nukunya, 2003). The joy of couples is to have children after marriage since 'voluntary childlessness' cannot be found in the dictionary of people in Ghana. According to Larsen (2000) the primary infertility rate for women in Ghana is estimated to be 2%, the secondary infertility rate was 14%.

Information on male infertility in Ghana is very scanty except that in a reproductive health report to the World Health Organisation in the year 2003, the Ghana Health Service (GHS) reported that male infertility was emerging in the Upper East Region of the country.

In Ghana, a number of studies have reported psychological distress among infertile women. Infertility-related stress and stigma were found among women seeking infertility treatment in Southern Ghana (Donkor and Sandall, 2007; 2009). The authors reported that 23% of the women experienced moderate stigma and 41% experienced severe infertility-related perceived stigma. Women who reported severe levels of perceived stigma had the highest mean score for fertility-related stress. Furthermore, two recent studies in Ghana reported on the mental health effects of infertility among Ghanaian women (Fledderjohann, 2012; Naab et al., 2013). According to these studies infertile Ghanaian women experience many psychosocial consequences of childlessness such as social stigma, marital instability and mental health problems including worrying, crying for long periods, and insomnia (Fledderjohann, 2012). Similarly, 53% of women seeking treatment for fertility problems in Ghana were depressed (Naab et al., 2013). Some individuals facing infertility who cannot withstand the high stigma on childlessness in Ghana also end up taking their own life.

This confirms previous statements that the consequences of involuntary childlessness are usually more dramatic in developing countries when compared to Western societies, particularly for women (Dyer et al., 2004; 2005; Ombelet et al., 2008; Van Balen and Bos, 2009).

Treatment seeking behaviour of childless couples in Ghana

In Ghana, apart from biomedical causes of infertility, traditional or religious causes of infertility such as spiritual and witchcraft have been cited (Donkor and Sandall, 2009). Consequently, in the treatment of infertility, many women resort to traditional healing and spiritual mediation (including churches) as well as orthodox biomedicine. Some women are

deeply convinced of supernatural causes, and so they patronize the services of traditional and religious healers for spiritual redress. At present it is very common in Ghana to see some women testifying in churches to the fact that they have been able to conceive and given birth through prayers. Women therefore form the majority of attendants at prayer camps and other alternative health care sources in Ghana's pluralistic health context (Sackey, 1999).

Even when medical means are used, it is mostly the traditional healers that get a lot of patronage in view of certain practices in the country and the perception that their services are cheaper. The irony of the situation is that Hospitals are not allowed to advertise themselves in the media but traditional healers and churches are free to do any adverts in any media and so they make all sorts of claims regarding their ability to treat infertility. The resort to spiritual and traditional healing in the end worsen the plight of many people living with infertility since they waste a lot of time doing these and in the end may have to rely on donor gametes for conception which increase the cost of treatments.

In the face of all these, a question that one can pose is "what support systems are there in place for childless persons, particularly women, in Ghana?" In the developed countries there are support groups, infertile couples receive professional information and counselling. However, in a strong pro-natal society like Ghana such support groups are non-existent. This situation can aggravate the situation of childless couples and individuals living with infertility in Africa.

It is therefore of uttermost importance that Counselling and Public Education are integrated seriously in infertility care in Africa and this can be best done if patients organisations are involved.

Should the focus be on women in Africa?

It is true that women are the highest hit when it comes to dealing with issues relating to infertility and so they are used mostly in advocacy and are often seen telling their stories. A typical African man irrespective of level of education hardly believes he can be faced with infertility and so use every possible means, whether good or bad, to get a child in an effort to "prevent a disgrace". The belief that men cannot be faced by infertility is generally accepted by many societies in Africa including Ghana. I believe the focus should be on the men more than the women in Africa in our advocacy and public education work. Once men understand infertility situations, they'll pull the women along and they'll all be happy people and children will be secondary issue.

Need for accessible infertility care in Ghana

Financial constraint has been seen as the key factor preventing infertile couples from accessing the treatment they need. Numerous people living with infertility in Ghana who now look to us for hope because we have made them aware about the emergence of an affordable fertility treatment through The Walking Egg project (Ombelet, 2013; 2014; Van Blerkom et al., 2014).

According to the Ghana Statistical Service (GSS) infertility and childlessness are probably the most important reasons for divorce in Ghana. Accessible infertility care can therefore help to reduce if not eliminate childlessness related divorce and poly-gamy in Ghana. Accessible infertility care can help reduce this.

Infertility brings domestic violence among couples and extended family relations. Accessible infertility care can help reduce this.

Infertility sometimes makes people poor because people sell their properties and other belongings to search for a child. Accessible infertility care can help reduce this.

The high stigma on childlessness in Ghana brings psychological problems to many couples and individuals facing infertility and this make some people commit suicide sometimes. Accessible infertility care can help reduce this.

Conclusion

Due to the severe socio-cultural and economic consequences of childlessness and infertility in Ghana, there is an urgent need for accessible and affordable high quality infertility care.

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Affordable ART in Kenya: The only hope for involuntary childlessness

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Introduction

Infertility is one of the key components of Reproductive Health, yet it remains an entirely neglected problem in Kenya. Data on infertility in Kenya and much of Sub Saharan Africa is scanty though the few existing studies show that the region is grossly affected by the problem of infertility. In his study on global access to infertility care in developing countries Ombelet (2012) states that more than 180 million couples in developing countries suffer from primary or secondary infertility In Kenya, the overall rate of subfertility was 26.1% among gynaecology consultations, with 50% attributed to tubal factors and 15% due to male factors (Murage A et al., 2011). This is still grossly underestimated taking into consideration that due to the stigma and myths of the disease, the couples seeking alternative care from religious sects, witchdoctors, herbalists and those whose quest for a child ends at the diagnosis of infertility.

Kenya has a population of 38.6 Million people with a total fertility rate of 4.6 % in 2009 (KDHS, 2010). In a country whose main priority is to reduce the growing population size through government and donor funded reproductive health programmes in support of contraception and safe abortions, it is not surprising that Kenya has no provision for public fertility care. It is simply not a priority. The debate surrounding infertility care in developing countries has been that, for countries burdened by high growth rates and poverty, focus should be on contraception and other population control programmes. However, there is no evidence from developed countries where infertility care is mainstreamed that links infertility care to increased population growth. In fact, evidence suggest the opposite since countries like Egypt have been highly successful in controlling population growth by integrating contraception services with infertility care for childless couples (Serour at al., 2008).

Currently there are six private fertility centres in Kenya, performing a total of approximately 900 IVF/ICSI cycles per year. The global need for IVF services has been estimated to be at least 1,500 cycles per million (Ombelet et al., 2008). We have a huge unmet need. One of the reasons to poor accessibility is the high cost of IVF/ICSI, with the lowest cost per cycle being $4500 per treatment. In a country where the poverty levels remain at 42%, as estimated by a 2013 World Bank report, the cost of ART is out of reach for many, making the dream of a child for the infertile couple painfully impossible.

Ironically, the less educated, rural-poor Kenyans and those living in urban informal settlements face the most devastating consequences of infertility. In the African context and still largely in Kenya the significance of a woman is solely defined through motherhood. Childless couples in Sub-Saharan Africa face the most severe negative psychosocial consequences and childless women are frequently stigmatized, isolated, ostracized, disinherited and neglected by the entire family and even the local community (Daar and Merali, 2002). The family, including siblings, parents and in-laws are deeply disappointed for the loss of continuity of their family and contribution to their community. This amplifies the guilt and shame felt by the infertile individual. This often results in polygamy and severe physical and psychological violence mitigated towards the woman, driving some infertile women to suicide (Anonymous, 2006). Additionally, emerging evidence suggests that infertile women, especially in Sub-Saharan Africa, are more likely than fertile women to be exposed to the HIV as a result of extramarital attempts to conceive (Bentley et al., 2000). Men also suffer stigma from their

infertility. Male infertility (estimated to be the cause of infertility in up to 50% of cases) is often deeply hidden in most societies because it is among the most stigmatizing of all male health conditions (Inhorn, 2000). Unintended childlessness is associated with overwhelming pain and grief that is often underestimated.

Fertility care is a basic right for every human being. At the United Nations International Conference on Population and Development in Cairo, Reproductive Health was defined as people having the right to decide when to have children, the number and the means to do so. This reproductive autonomy has been the main argument in favour of the provision of infertility treatment in developed countries. If citizens of developed countries enjoy this right, why would citizens of developing countries not have the right to have at least one child, especially if infertility care is made more affordable for a much larger part of the population (Ombelet, 2012)? If overpopulation was the threat, would accessibility to infertility treatment in developing countries account for more than 1% of all deliveries (Ombelet, 2011)? Given that inclusivity principles are universally encouraged in building a cohesive society, does ignoring infertile individuals amount to social justice and equity? Finally, does the presence of more pressing health needs coupled with the challenge of limited resources warrant total disregard to infertility treatment?

The only true hope for most Kenyans struggling with unintended childlessness lies in the introduction of affordable ART services. The challenge is to reduce the costs of medication and the equipment set up cost of the ART laboratory. Modified natural and mild stimulation IVF protocols have not yet been implemented in Kenya. This approach may be the only feasible solution to the infertile couple especially since the burden of infertility is largely attributed to bilateral tubal occlusion, which is bypassed by this technique. ART at an affordable cost would allow couples to seek fertility care early before age related ovarian factors affect favourable outcomes. Modified natural and mild stimulation IVF with single embryo transfer will also address some of the costly complications of conventional IVF such as multiple pregnancy, ovarian hyper-stimulation syndrome and premature new-borns. The use of equipment that can be purchased at lower prices, and possibly simpler, less costly laboratory and clinical infrastructure also serve to reduce the overall cost.

The only foreseeable barrier to low cost ART is adequately trained personnel. Currently, in Kenya there are less than ten well-trained IVF specialists and no adequate trained embryologist. Most centres hire an expatriate embryologist who charges a very high rate per patient per cycle, forcing these centres to operate in ART batch cycles to reduce on costs. We must train interested Kenyans if we truly want to implement and sustain affordable ART in the near future.

The extensive attention ART is receiving around Kenyan media, as we are currently debating on the legislation of ART, will hopefully serve to sensitize the public on the need for affordable fertility care. Egypt has made remarkable progress in integrating ART into the public sector through government support and subsidies that ensure infertile couples receive a chance to become parents. Low cost fertility services in Kenya may make access feasible in at least some settings and drive the momentum for government involvement. Affordable ART in Kenya will give the much need hope to the now hopeless couples struggling with involuntary childlessness.

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Semen analysis workshops: 17 years' experience

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Abstract

The study reports on the results recorded during a series of semenology workshops presented from 1997 to 2014. The results were obtained from training workshops that were conducted in 6 continents in 38 cities including 1124 individuals. All workshops consisted of 2 sessions namely a pre-and post-training session. Results recorded from the pre-training sessions were used as a baseline value of current knowledge. In most cases pooled fresh or cryopreserved semen samples were provided by the organizing institution. The mixed effect linear regression model showed a significant decrease in the mean scores from the pre-training scores, $p < .001$. Training of technicians as well as regular proficiency testing will ensure continuous communication with the referring laboratory.

Key words: **Examination, semen, technicians, training.**

Introduction

The value of a standardized semen analysis remains an important diagnostic tool and when properly done should guide clinicians to an appropriate therapeutic approach (Keel, 2002; Keel, 2004). This is especially true for developing countries that are often in distant rural areas without the necessary clinical and laboratory resources. Unfortunately the results of the semen analysis are often unreliable due to inter-and intra-technician variations that are caused by the lack of trained or inexperienced laboratory staff. Several factors are responsible for this technical variation including differences in the methods used and differences in proficiency among technicians. These differences in methodologies between laboratories are well documented (Ombelet et al., 1998), but since the publication of the WHO 2010 manual the between-laboratory variation should be negated in case the relevant individuals responsible for the analysis of semen are well trained. Intra-and inter-individual variability should therefor decrease to non-significant levels. This report provides information on semenology training workshops that were conducted in 6 continents in 38 cities including 1124 individuals.

Materials & Methods

All workshops consisted of 2 sessions namely a pre-and post-training session. In most cases pooled fresh or cryopreserved semen samples were provided by the organizing institution. Participants were divided into pairs each manning a semen work station. The workstations were equipped with a bright field/phase contrast microscope with 20×, 40× and 100× objectives. Prior to the training participants were requested to record the values for morphology (% normal cells), concentration, motility and vitality. Morphology recordings were done on Hemacolor (Merck Chemicals, Cat no 1.11661./1) or Papanicolaou stained slides. Sperm concentrations and motility were done on the supplied semen samples. The results of the pre-and post-training sessions were compared with the values recorded for the reference slides by an experienced andrologist.

Following the pre-training evaluation session delegates were lectured on the WHO guidelines on the analysis of human semen. During the morphology training session's high quality micro-photographic images of numbered sperm were projected on a large screen. Individual spermatozoa were discussed

during group session to underline the specific aberrations responsible for the sperm to be classified as abnormal. Sperm concentration and motility were also explained using video clips of counting chamber grids as well as motile sperm samples, respectively. The results of the morphology training program for example were as follows: The pre-training slide contained 17% normal forms while the delegates recorded 46.1 ± 22%, while the post training slide contained 12% normal forms while the delegates reported 8.6 ± 10%.

Statistical analysis

The mixed effect linear regression model showed a significant decrease in the mean scores from the pre-training scores, $p < .001$. The adjusted mean scores were calculated from the mixed effects model. The post mean is equal to -0.19 with 95% confidence interval of -0.98 to 0.61. Since this interval spans 0 it shows that the mean morphology reading after training by the participants was not significantly different from 0. After training the participants read the morphology slides close to the true value. In contrast the pre- training readings were substantially biased – the Z-score of 6.5 indicates this (Fig. 1).

Results

Morphology: External quality control

Since 1997 our experience indicated that hands-on training provides satisfactory results as far as maintenance of technical skills during the evaluation of morphology, sperm concentration, and vitality is concerned. During a series of workshops the department of Obstetrics & Gynaecology at Tygerberg Hospital in conjunction with the World Health Organization's Special Programme for Human Reproduction (HRP) initiated an external quality control programme for Sub Sahara andrology laboratories (Franken et al., 2000). In that programme 15 of the 19 participating individuals (78%) consistently reported sperm morphology readings for example over a 40 month period within ± 0.5SD limits of error. The results of the external quality control study were used to record the technical reading skills for morphology and the participants were classified according to their results over the 40-month period.

Poor reading skills

If 50% readings, recorded over the 40-month period were inside the limits of error i.e. the ± 0.5SD-score,

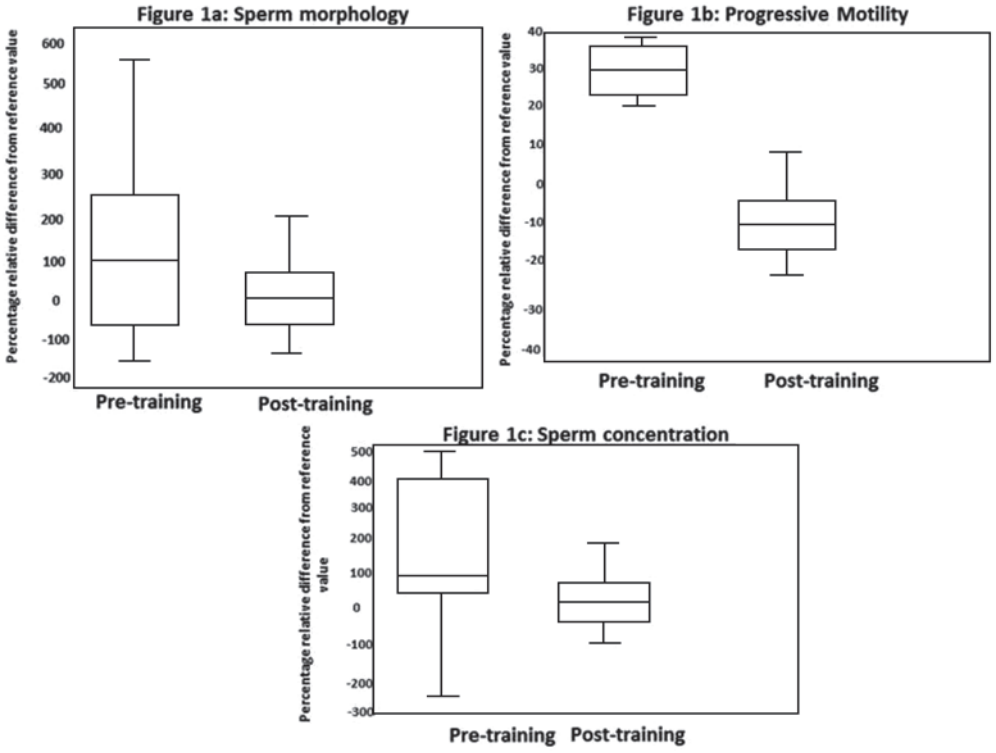

Fig. 1. — Pre- and post-training: Percentage normal sperm, sperm concentration and progressive motility values recorded by laboratory technologists'. Box–Whisker plots illustrating the percentage difference from the reference value.

marginal reading standards were assumed. We recorded 5.7% of participants in this category.

Marginal reading skills

If 51-60% readings recorded over the 40-month period were within the ± 0.5SD-score, marginal-to-good reading skills were assumed. We recorded 11.3% of participants in this category.

Good reading skills

If 60-69% of the readings, recorded over the 40-month period, fell inside the limits of error i.e. the ± 0.5SD-score, good reading standards are assumed. We recorded 83% of participants in this category.

The results recorded by the delegates for the percentage sperm with progressive motility and sperm concentration are depicted in Figure 1. In both motility and concentration evaluations the pre-training results were vastly overestimated. Overestimation seems to be more of a problem with high-concentration specimens (Brazil, 2010). As far as the evaluation of sperm concentration is concerned the results during the pre-training session showed a wide variation amongst the delegates.

Discussion

Training of technicians as well as regular proficiency testing will ensure continuous communication with the referring laboratory. Proficiency testing of technician skills is of the utmost importance if andrology laboratories want to secure a professional code of conduct. The authors firmly believe that global quality control measurements in andrology laboratories will eventually become mandatory. A high quality semen analysis still represents the cornerstone in the investigation of the infertile couple. In order to maintain low intra- and inter-technician variation and high quality proficiency testing among laboratory technicians, continuous teaching programmes should be available to all.

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Prevention of infections in an ART laboratory in a developing country

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Introduction

"Any uncertainty about a future event that might threaten an organization's ability to accomplish its mission" may be labelled as a risk. Proactive prevention as opposed to reactive cure can be seen as prophylactic management to provide quality assisted reproduction technology (ART) services (Mortimer and Mortimer, 2005). Reactive actions such as timeously troubleshooting with corrective adjustments and evidence-based handling of adverse events during ART procedures are also invaluable risk management tools.

Developing countries are constrained by limited access to, or availability of resources, which will impact on the screening, diagnosis and management of infectious diseases. The 2014 West African Ebola outbreak is a current example, with numerous media reports outlining the prevailing stigma and conspiracy theories on the origin and progress of the disease. Undoubtedly disgrace, ignorance, limited finances and resources similarly impede the extent and frequency of screening for sexually transmitted infections (STIs) prior to ART, selection of ART procedures, and choice of a private or public ART provider in low to middle-income countries (Huyser and Fourie, 2010). The aim of the current paper is to discuss the prevention of infections in a laboratory-orientated ART setting in a low to middle-income country, with reference to simplistic risk reduction applications to avoid the introduction and transmission of pathogens. The diagnostic and procedural phases will be briefly discussed, as indicated in Figure 1, i.e. (i) patient evaluation and screening for microbes and (ii-iii) the prevention of procedural and environmental contamination including sperm preparations to reduce infectious agents.

Patient screening for microbes: detection and prevention

Work-up of couples prior to ART treatment and handling of human bodily fluids (blood, follicular fluid and semen) during procedures should be generic for all patients, irrespective of the type of ART procedure (Huyser, 2014). Various viral agents such as cytomegalovirus, hepatitis B (HBV), hepatitis C (HCV), herpes simplex virus type 2, human T-lymphotrophic virus, and human immunodeficiency virus (HIV) can be transmitted through semen and vaginal secretions (Elder et al., 2005). A detailed review and guidelines of infections in the female and male partner, and infectious complications of ultrasound-guided oocyte retrieval is provided by Steyaert et al. (2000).

The practice of routine microbial semen cultures in asymptomatic couples is debatable; however patients should be routinely screened for HIV, HBV/HCV (blood plasma) as well as other predominantly prevalent STIs (in the region) and laboratory personnel notified of the test results prior to the ART attempt (Magli et al., 2008).

Sexual health screening in most developing countries where ART is offered, is probably less state-regulated with infrequent and fewer tests over time. Most ART practices in developing countries use point-of-care testing that offers overall affordability, and a short time-span to perform, interpret and provide the results. The use of rapid STI-screening tests with high sensitivity, specificity and long shelf-life presently plays a significant role in infectious disease screening and reproductive health management in resource-constrained countries (Huyser and Fourie, 2010). Technological advancement of currently available rapid tests is needed e.g. direct assessment in seminal plasma as

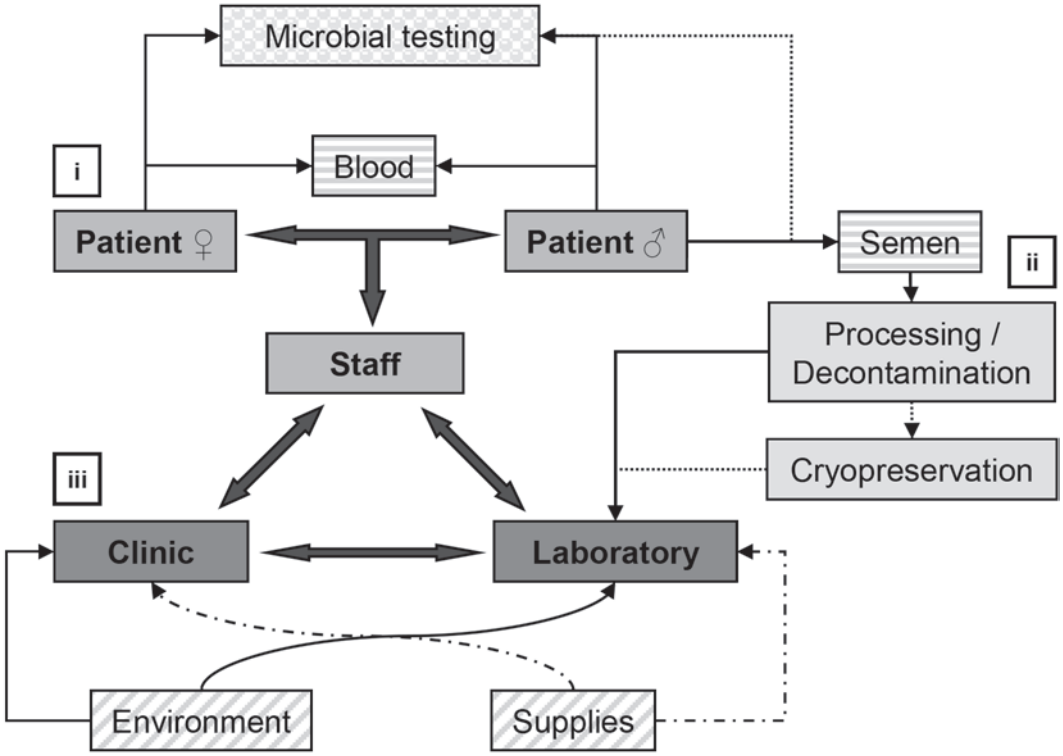

Fig. 1. — *Elements that influence the prevention of infections during an ART program:* (i) Diagnostic phase, i.e. patient assessment and screening, and (ii-iii) the procedural phase including sperm processing, environmental and technical factors (Huyser, 2014).

well as blood plasma, with the ability to grade viral load levels to a certain degree.

Laboratory procedures and staff conduct eliminating and reducing the transmission risk of microbes during ART procedures should be a central theme during training, especially when resources to test or monitor aspiring ART patients are lacking or infrequently provided.

ART procedures: gametes and embryos

Environmental and technical factors

ART laboratory personnel are trained to "treat each sample as potentially infectious" and "to ensure aseptic conditions for gametes, zygotes and embryos" (Magli et al., 2008). Safeguarding through universal precautions and adherence to the safety procedures outlined in the WHO laboratory manual for the examination and processing of human semen (WHO, 2010) is usually provided as guidelines when in doubt. To take extraordinary preventative action implies having knowledge of threats and the degree of risk involved consequently. Awareness and understanding of the vulnerabilities of the ART system wherein laboratory personnel function are invaluable assets when unforeseen equipment failure occurs or instant decisions have to be made to safeguard procedures. Simple laboratory organisational precautions include uncluttered work surfaces, phasing out of sharp-edged glass items, no mouth pipetting, hygienic working conditions (procedures using appropriate equipment and disposables), regular cleaning and decontamination of the laboratory (quality control measures), proper (hazardous) waste disposal and strict access control to different laboratory sections. On a personal level, skin breaks should be protected with waterproof dressings and non-toxic powder-free gloves should be worn at all times, together with appropriate atire (barrier precautions - clothing, masks, gowns, and goggles) (Steyaert et al., 2000; Elder et al., 2005; Magli et al., 2008). Personnel should be immunized against HBV with a baseline serum result available (Elder et al., 2005) as well as against other viral diseases for which vaccines are available (Magli et al., 2008).

Biosafety for ART procedures are classified as level 2, with supplementary precautions when processing HIV and HBV/HCV-positive samples. It is prudent to ensure separate facilities and equipment for semen handling and cryopreservation within an ART laboratory (Elder et al., 2005). Additionally specimens from patients who tested positive for blood borne viruses should be processed, cryopreserved and stored in dedicated areas using

separate storage tanks with adherence to specific safety measures (Magli et al., 2008). Alternatively seropositive patients can be batched or scheduled to allow sufficient decontamination of the laboratory (Magli et al., 2008) after contact with patient's body fluids, i.e. semen processing, follicular fluid-aspirations and embryo transfer. All procedures and manipulations that can produce aerosols or splatter should be performed in Class II biological safety cabinets (BSCs) with vertical laminar flow, using aseptic techniques and sterile disposables (Elder et al., 2005; Magli et al., 2008). Most ART laboratories in developing countries only have one BSC for all laboratory material processing, a single centrifuge, stereo microscope, with open bench sperm processing. Batching and staggering of laboratory activities in the BSC according to a workable timeline can stratify and spread activities out in a safe manner. In addition, microdroplet cultures under oil (Magli et al., 2008) should speedup embryo evaluation and protect the culture medium from environmental contaminants when only large upright incubators are available; and/or air filtration or a positive pressure system is *not* available. These preventative actions are especially applicable in humid tropical countries where apartments or houses are modified and adapted to function as ART units.

Cryopreservation is often an expensive necessity during ART in developing countries. An array of protocols, devices and publications on biosafety trials outlining the potential for disease transmission and pathogen survival during cryopreservation are currently available. If a cryopreservation protocol could be designed that can be universally applied, the worldwide use thereof could translate in an economical and safe system (Scholz, 2012). According to Scholz (2012) commercial liquid nitrogen does not pose a sufficient high risk for contamination, whereby prevention of cross-contamination in containers using closed or semi-closed vitrification devices that permits sealing as well as a high cooling rate should be sufficient to warrant sterility, good survival and development of the specimen cryopreserved.

Semen processing: Decontamination procedures

Semen samples should be handled with extreme care as a biohazard by laboratory personnel (WHO, 2010). In-house statistics have indicated the positive identification of microbes in approximately 50% of all semen samples obtained for ART procedures, with gram-negative species present in only a fraction of samples (Huyser and Fourie, 2010; Fourie et al., 2012). In addition, over 50% of all neat semen samples from HIV-1 infected males tested consistently positive for HIV-1 RNA (quantitative result) or DNA (qualitative result) over a 5-year period (Huyser and Fourie, 2010; Fourie et al., 2014) (Table I – revised data).

Antimicrobial treatments are prophylactic or empirically prescribed to intended ART patients when pathology services are not readily available to the couple. Sperm purification through discontinuous density gradient centrifugation is used, in preparation for intra-cytoplasmic sperm injection (ICSI). In this scenario seroconcordant or discordant couples are restricted to the ICSI procedure with confounding costs; in cases where ICSI is not offered at the ART Unit the couples have to add travel and accommodation costs.

An array of sperm processing methods are commercially available, from simple office-based semen preparation kits for intra-uterine insemination to density gradient centrifugation with an additional mechanical device to reduce microbe recontamination in the processed sample (ProInsert™ system, Nidacon, Sweden) (Huyser and Fourie, 2010; Fourie et al., 2014). Once the enriched sperm fraction is removed, the device can be capped and discarded as biohazardous waste. In our program, semen decontamination eliminated HIV-1 RNA (100% non-detection) and proviral DNA from 98.75% of semen samples of HIV-1 positive patients, as shown in Table I. A robust and affordable semen decontamination method is a valuable risk reduction tool to eliminate bacteria (Fourie et al., 2012) and viruses (Huyser and Fourie, 2010; Fourie et al., 2014) within a low-resource setting.

Table I. — HIV-1 RNA and DNA detection in neat semen and purified sperm samples from HIV-1 positive males (N = 104) in preparation for an ART cycle.

Neat Semen Samples (N = 236)				Processed Sperm Samples (N = 160)	
Negative	Positive			Negative	
DNA & RNA	DNA	RNA	DNA & RNA	DNA	RNA
46.19% N = 109	15.68% N = 37	19.91% N = 47	18.22% N = 43	98.75% N = 158	100% N = 160

Conclusion

The prevention of infections within any ART laboratory is a team effort which starts with the couple's reproductive health work-up to identify and avoid vertical and horizontal transmission and nosocomial transfer of pathogens during an ART cycle. Infection management forms part of quality control and risk reduction. Minimizing or averting risks implies having the tools and experience to recognize the consequences and likelihood of threats within a laboratory. Semen decontamination will reduce contamination risks, but will not eliminate all infectious agents from semen. Cost-benefit risk prevention and reduction tools created for ART laboratories in developing countries can equally benefit ART laboratories in developed countries.

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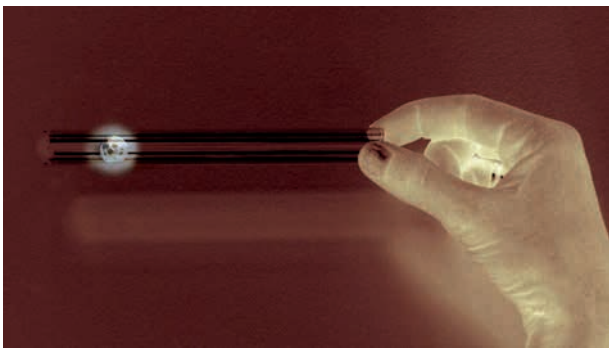

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Evidence-based IUI in developing countries

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Abstract

Intrauterine inseminations (IUI) are easier to perform, less invasive and less expensive than other methods of assisted reproduction. The rationale for the use of artificial insemination is to increase gamete density at the site of fertilisation. It is generally accepted that IUI with homologous semen should be preferred as a first choice treatment above more invasive and expensive techniques of assisted reproduction in case of cervical, unexplained and moderate male factor subfertility. Scientific validation of this strategy is difficult because the literature is rather confusing.

Effectivity has been documented in controlled studies under the condition that the inseminating motile count exceeds more than 1 million motile spermatozoa. Risks and costs are minimal, provided the multiple gestation incidence can be reduced to an acceptable level and provided at least one tube is patent. Training is easy and severe complications are almost non-existing.

Reasons enough to promote the use of IUI as a valuable first line treatment for most cases of non-tubal infertility in developing countries.

Key words: **Artificial insemination, assisted reproduction, human, intrauterine insemination, IUI, semen, semen quality.**

Introduction

Contrary to IVF/ICSI methods, IUI is easy to perform, inexpensive and offers particular advantages such as the minimal equipment required, an easy technique to learn, being less invasive with a reduced psychological burden on the couple when compared to IVF/ICSI. Subsequently IUI has a good couple compliancy (low drop-out rate), a low risk for OHSS (ovarian hyperstimulation syndrome) and a low multiple pregnancy rate in natural cycles and clomiphene citrate or low-dose HMG (human menopausal gonadotrophins) ovarian stimulation protocols (Ombelet et al., 2008).

Although there is a lack of good quality studies on IUI performance, we will try to make an overview of the actual evidence-based data on different levels of IUI practice.

Indications for IUI

Cervical factor

In case of an isolated cervical factor, defined as a repeated negative post-coital test despite a normal semen quality and adequate timing, IUI in natural cycles significantly increases the probability of conception (Steures et al., 2007).

Male factor subfertility

In a Cochrane review it was clearly shown that there is insufficient evidence to conclude whether IUI is effective or not in moderate and mild male infertility (Bensdorp et al., 2007). Older evidence, often from cross-over trials, found a significant beneficial effect of IUI.

Unexplained subfertility

It seems that natural cycle IUI has no significant beneficial effect over expectant management in case of unexplained infertility (Verhulst et al., 2006). On the other hand the combination of ovarian stimulation and IUI significantly improves live birth rates in couples with unexplained infertility (Verhulst et al., 2006), but we have to take into account that the ovarian stimulation regimen in a lot of these studies was rather aggressive resulting in high multiple pregnancy rates. In a recent economic analysis it was shown that IUI-ovarian stimulation is the preferred treatment to start with in case of unexplained infertility. When IVF-eSET (elective single embryo transfer) results in a higher ongoing pregnancy rate (> 38%), IVF would be the preferred treatment (Van Rumste et al., 2014).

Semen quality and IUI

The four sperm parameters that are most frequently examined were the following: (a) the IMC (inseminating motile count after washing), (b) sperm morphology using strict criteria, (c) the TMSC (total motile sperm count in the native sperm sample) and (d) the TM (total motility in the native sperm sample).

It was clearly shown that a score of more than 4% normal morphology using strict criteria is needed to result in a significantly higher pregnancy rate per cycle (Van Waart et al., 2001; Ombelet et al., 2003). According to Ombelet et al. (Ombelet et al., 1997; 2014) an IMC of 1 million can be used as a reasonable threshold level above which IUI can be performed with acceptable pregnancy rates. For the TMSC and the TM a cut-off value of 5 to 10 million and 30% was most frequently reported respectively.

Ovarian stimulation and prevention of multiple pregnancies

IUI in combination with mild ovarian stimulation is effective in couples with unexplained subfertility, minimal to mild endometriosis and mild male subfertility. According to a risk analysis by van Rumste et al. (2008) one should aim for a maximum of two dominant follicles in order to avoid high-order multiple pregnancies.

Clomiphene citrate remains the first-choice drug to use although CC might have a negative effect on the endometrium. If needed HMG or recombinant FSH can be used in dosages of 50-75 IU per day. Strict ultrasound monitoring of each stimulated cycle is mandatory. One should strive after two dominant follicles larger than 15 mm but all follicles larger than 10 mm should be measured and taken into account when defining cancellation criteria.

Timing and number of IUIs per cycle, bedrest after IUI

Adequate timing of the insemination seems to be essential. According to the current available a time frame from 12 to 36 hours after HCG injection can be used (Cantineau et al., 2009).

One study reported a positive effect of double insemination in couples suffering from male subfertility (Liu et al., 2006). Double IUI should only be advised when proven effective, since a second IUI will increase the costs and psychological burden.

According to two prospective randomized trials 10-15 minutes immobilization subsequent to intrauterine insemination significantly improves cumulative ongoing pregnancy rates and live birth rates (Saleh et al., 2000; Custers et al., 2009).

Semen preparation techniques (SPT)

In a Cochrane Review (Boomsma et al., 2012) there was no clear evidence which sperm washing technique is superior when clinical outcomes after IUI are investigated.

Although DGC showed to be superior to swim-up and wash technique concerning laboratory outcomes (e.g. semen parameters) there is insufficient evidence to recommend any specific SPT when speaking about clinical outcome after IUI.

Fallopian sperm perfusion

In fallopian tube sperm perfusion (FSP) a larger volume (4 ml) of inseminate is used when compared to regular IUI (0.3-0.5 ml). The rationale behind FSP is to create a sperm flushing of the tubes and an overflow of motile spermatozoa closer to the eggs (Kahn et al., 1993).

Because of the promising results in many studies I believe that a well-powered multi-centre prospective randomized trial comparing pregnancy outcome of FSP (without Foley catheter) with regular IUI in case of unexplained and moderate male infertility should be performed.

Conclusion

Treatment with artificial insemination with husband's sperm remains a valuable first choice treatment before starting more invasive and more expensive techniques of assisted reproduction in

many cases of human subfertility, at least if tubal patency is proven. It is a simple and non-invasive technique which can be performed without expensive infrastructure in poor-resource countries.

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Excellence needs training "Certified programme in endoscopic surgery"

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Introduction

Since the early 1990s, laparoscopic surgery has been implemented in nearly all surgical disciplines. On one hand, it offers the possibility to improve the surgical outcome and patient compliance, but on the other hand, it demands the surgical community to train and acquire specific skills. The laparoscopic surgeon needs to work in a keyhole environment, it demands the ability of depth appreciation on a two-dimensional screen, hand-eye coordination, bimanual coordination, ambidexterity, and handling long instruments from a fixed position and the surgeon has no tactile feedback. Laparoscopic techniques might even be related to an increased patient's morbidity and mortality if not performed by properly trained surgeons (Van der wal, 2007; Campo et al., 2012a; Gala et al., 2013; Palter et al., 2013).

Training in surgery is challenged and it seems logical, but not yet implemented that a future laparoscopic surgeon needs to have specific theoretical and practical knowledge and skills prior to perform a laparoscopic surgical intervention.

A structured educational concept is needed and should provide an answer to the problem of the excessive long learning curves in the operating room, the limited accessibility of theoretical and practical endoscopic learning programmes and the lack of a universal accepted and validated system of certification and credentialing.

The apprentice-tutor model was useful for many years, but the complexity of the modern surgical technology requires specific skills, to be taught also outside of the operating theatre. Based on the newest clinical and scientific evidence, the European Society of Gynaecological Endoscopy (ESGE) together with the leading European and American professional organizations have recommended in a joint statement that every hospital should provide dry lab endoscopic training and testing as a means to enhance the quality of patient care (Gala et al., 2010; Campo et al., 2010, 2012b; Burden et al., 2011; Hur et al., 2011; Palter et al., 2013) (Fig. 1).

The ESGE has furthermore in collaboration with the European Academy of Gynaecological Surgery (+he Academy), elaborated a well-balanced diploma curriculum, called Gynaecological Endoscopic Surgical Education and Assessment (GESEA) programme (EAGS, 2014; ESGO, 2014). The programme is founded on the evidence that an endoscopic surgeon requires 2 different skills sets. On one hand, the instrument handling skills and on the other hand, the surgical competences. The endoscopic skills follow a different learning path than the surgical, it is a learning process like swimming which does not require the presence of a highly skilled endoscopic surgeon but the ability remains over a long period of time. It is seen as a necessity to master those skills prior to the in OR surgical training programme (Campo et al., 2010, 2012a, 2012b; Molinas et al., 2010; Palter et al., 2013).

Surgical competence is a continuous learning process and follows the learning characteristics of learning a language; it takes advantage of the one to one learning with a highly skilled surgeon and demands for continuous practice and experience.

The GESEA diploma programme has integrated those findings in a structured, educational training route trying to provide an answer to the current challenges of surgical education (EAGS, 2014; ESGO, 2014).



Fig. 1. — Joint recommendation on endoscopic training and quality assurance

Certification and Diploma in endoscopic surgery

The GESEA programme is based on 3 levels of expertise and for each level different areas of competence have to be achieved in a well-defined ranking order, first the certificate exam has to be passed hereafter one can accomplish the requirements for the diploma of the corresponding level (Fig. 2).

First level refers to the Bachelor in Gynaecological surgery
Second level refers to the Minimal Invasive Gynaecological Surgeon (MIGS)
Third level refers to the Master in Hysteroscopy and the Laparoscopic Pelvic Surgeon.

Bachelor Diploma

1. *Get your theoretical Star*

The entry gate to the programme is a free online e-learning tutorial programme made by +he Academy winners project and published on the virtual university of WeBSurg. Each tutorial is followed by a quiz session and after accomplishing all the questions correctly the first star of your curriculum is achieved.

2. *Get trained and tested in endoscopic skills*

Every endoscopic surgeon needs a minimum of practical skill lab training before going into the OR. It is scientifically proven that it improves endoscopic surgical performance in the operating room, increases patient's safety and improves the surgical learning process. The practical training and testing models of +he Academy seems to correlate very well with the necessary skills required for laparoscopic surgery.

The current scientific evidence shows that full acquisition of laparoscopic psychomotor skills tested with the LASTT method (Fig. 3) facilitates the acquisition of more complex laparoscopic tasks like knot tying tested with the SUTT method. Even more important is the observation that training programs on knot tying only are insufficient to acquire the full proficiency in laparoscopic

Winners 1st Star Bachelor	LASTT SUTT - E-knot HYSTT	TESTT 1	LASTT SUTT 1 HYSTT 1	Certificate 1 Bachelor in Endoscopy	Observer Observation of 30 endoscopic procedures. Self-testimonial, no official document required.	ESGE annual congress or +he Academy workshops eg. CME points will be determined by EBCOG / UEMS.	Level 1 Diploma ESGE Bachelor in Endoscopy
Winners 2nd Star Minimal Invasive Gynaecological Surgeon	LASTT SUTT - E-knot HYSTT	TESTT 2	LASTT SUTT 2 HYSTT 2	Certificate 2 Minimal Invasive Gynaecological Surgeon	First Surgeon 50 ESGE level 3 laparoscopies 50 ESGE hysteroscopies, 10 myomectomy, 10 endometrial ablation, 20 polypectomy and 10 miscellaneous of ESGE level 2 or 3. Maximum period of 5 years. Official document required.	Annual presence at recognised endoscopic congress. Minimum attendance at one advanced endoscopic workshop.	Level 2 Diplomas ESGE Minimal Invasive Gynaecological Surgeon
Winners 3rd Star Master		TESTT 3a TESTT 3b	SUTT 3 HYSTT 3	Certificate 3 Laparoscopic Pelvic Surgeon Master in Hysteroscopy	Laparoscopic Pelvic Surgeon 50 level 4 laparoscopies. Master in Hysteroscopy 10 type 1 myoma, 10 type 2 myoma, 10 uterine septum, 5 Tuterus, 5 Placental remnants, 5 Ashermann, 5 miscellaneous like Adenomyosis, Fetoscopie or sectio scar surgery. Maximum period of 5 years. Official document required.	Annual presence at recognised endoscopic congress. Annual attendance at one advanced endoscopic workshop as tutor.	Level 3 Diploma ESGE Laparoscopic Pelvic Surgeon ESGE Master in Hysteroscopy

Fig. 2. — Overview of +he Academy certification and ESGE diploma programme



Fig. 3. — LASTT training and testing method

instrument handling and as such a structured training and testing programme should be provided (Campo et al., 2010, 2012a, 2012b; Molinas et al., 2008, 2010). A web based scoring platform provides the necessary training progress reports, benchmarking with positioning of individuals in relation to the peers. This online scoring platform (OSP) with validated benchmark data is the instrument for self and group evaluation. For each exercise the individual can receive his or her position to one of the 3 groups of excellences and whiting the group an individual ranking serves as a personal motivator the training process and exam preparation (Fig. 4).

3. *Get +he Academy Bachelor Certificate*

+he Academy has developed a certification programme consisting of a theoretical multiple choice exam called TESTT 1® and one session of three different practical exams the LASTT® for measuring the Laparoscopic Instrument handling skills, the SUTT 1® for measuring the basic stitching and knotting skills and the HYSTT 1® for measuring the basic hysteroscopic handling skills. Only if the mentee passes both the theoretical and practical exams, +he Academy Bachelor Certificate is received - this is the obligatory prerequisite to apply for the GESEA Bachelor Diploma. It is also seen as the minimal requirement a surgeon should have before entering in the one to one in OR training.

4. *Bachelor Diploma*

ESGE has defined that to become a Bachelor in endoscopic surgery, exposure to 30 procedures as an observer or in OR assistant and the attendance of a recognised workshop or congress in endoscopy is required.

Further diplomas

The same principles are used to enter and accomplish the second and third level in which the diploma of Minimal Invasive Gynaecological Surgeon (MIGS) is seen as the reference for any Gynaecologist

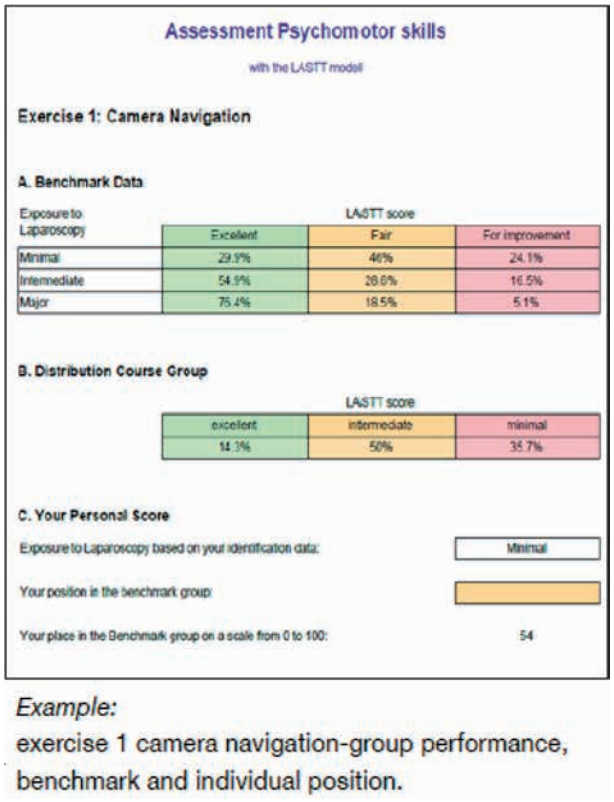

Fig. 4. — Online scoring platform example

performing routine laparoscopic surgeries like hysterectomy and myomectomy and hysteroscopic surgeries like endometrial ablation, polypectomy and type 0 myomectomy.

The laparoscopic Pelvic Surgeon is trained in supplementary abdominal surgical procedures with vascular, intestinal and urological dimensions. The Master in Hysteroscopy deals with the more difficult hysteroscopic procedures like the Ashermann syndrome, Intra myometrial surgery, foetal surgery etc.

Discussion

The implementation of an educational training and certification programme in laparoscopic surgery is a real challenge.

The actual pressure surrounding the surgical practice imposes evidently a validated quality control program. This control starts by a standardization of the surgical training. The European Academy succeeded to elaborate a program of training and certification dealing with both the theoretical knowledge on instrumentation, OR organisation, anatomy and complication management, and the practical laparoscopic psychomotor skills, including suturing and knot tying skills. It remains without doubt that this is only the first but an important step in a professional training program in laparoscopic gynaecological surgery.

Teaching institutions have to organise multi-disciplinary endoscopic dry skill labs as scientific evidence is provided skill training prior to in OR surgical training, reduces patients' morbidity and mortality in all endoscopic surgical disciplines.

To bridge the current need for an appropriate, accessible and cost effective gynaecological learning programme in endoscopic surgery, a free of charge online distance learning programme was established. Recently also access to the practical training and testing tools is made available. The Laparoscopic Skills, Suturing and Hysteroscopic Training and Testing method (LASTT, SUTT and HYSTT) provides through a web based "Online Scoring Platform" (OSP) the necessary feedback to mentors and individuals of their practical endoscopic skills training. A set of 10 exercises is now established for the 2 first levels and can be used in every dry skill lab at affordable cost. The research performed shows the validity of the exercises and demonstrates that the methodology used is independent of the presence of a high skill endoscopic surgeon and can be managed by an approved mentor. After training and testing to achieve the different certificates +he European Academy for Gynaecological Surgery has established a standardised and universally implementable theoretical and practical exam. This exam is provided at the annual congress of the ESGE, its corporate member society congresses and at licensed centres that have passed the mentor exams and the centre audit.

Conclusion

The tremendous development of knowledge, the introduction of high technology in medicine and the obvious tendency to super specialisation provides a major challenge to our 'custodians of knowledge' such as universities and scientific Societies.

Not only patients, but also physicians have the absolute right of access to all available knowledge in a structured and validated way.

As a result of intensive research coordinated by +he Academy with a multidisciplinary team of gynaecologists and surgeons, a unique structured training and certification programme in endoscopic surgery is established providing in an accessible way the first step in a global diploma programme in Gynaecological endoscopic surgery.

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The Walking Egg Project: how to start a TWE centre?

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Introduction

In the Walking Egg project we want to integrate infertility care within the concept of family planning, emphasizing that family planning centers shall be more successful if they pay attention not only in preventing unwanted pregnancies but also by promoting the chance of pregnancy in case of involuntary childlessness. Infertility treatment and family planning are in fact two sides of the same coin. Education, empowerment of women and economic prosperity are the most effective solutions to most problems related to both population growth and infertility. Reproductive autonomy, justice and equity support our efforts to make ART available and accessible worldwide subject to political stability and a basic level of medical infrastructure.

The main goal of the Walking Egg project is the implementation of good quality but low-cost infertility centres in developing countries (DC). Diagnostic and therapeutic procedures and protocols should be affordable, effective, safe and standardized.

Because resource-poor countries differ in their status of development, three levels of assistance were suggested (Sallam, 2008). A level 1 infertility clinic is a basic infertility clinic capable of offering the following services: basic infertility care including semen analysis, hormonal assays, follicular scanning, ovulation induction and IUI. In Level 2 infertility clinics IVF can be performed as well.

During many expert meetings it was decided that Level 3 infertility clinics capable of offering ICSI, cryopreservation and operative endoscopy are not part of the Walking Egg Project in the initial phase. Therefore our first target is the implementation of good quality level 2 centres.

Implementation of level 2 services entails the following activities (Sallam, 2008):

1. ***Equipping the clinics:*** Infertility clinics in developing countries should be provided with low-cost and easy serviceable equipment taking into consideration the local problems often encountered (e.g. fluctuating voltage, frequent power cuts, unavailability of servicing facilities, irregular supply of consumables, etc...). This may require negotiations with various manufacturers to supply these tools at affordable prices, particularly if large quantities are ordered.
2. ***Training the staff:*** This includes the training of the medical, paramedical as well as the administrative staff. Training courses should tailor to the local conditions and the possible difficulties encountered in developing countries. Table I gives an overview of the key topics covered in the training courses. Training, quality control, regular audit and systems of accreditation and registration should be implemented in order to maintain appropriate standards of care. Our objective is to organize a one or two week(s) course for all members of the team who are involved in the set-up of a pilot-centre, part of the Walking Egg Project. This training will need the support of experts in the field, who are capable to tutor the training courses at the highest level in a very short time, taking into account the experience of the trainees and the quality of facilities that can be expected in the new pilot-centres.
3. ***Educating the public:*** This necessitates establishing contacts and working relationships with schools, community leaders, traditional healers as well as the media, producing and distributing educational materials (brochures, posters and audio-visual material) etc.
4. ***Running the services*:** This should take into consideration staff salaries, regular purchasing of consumables, cost of equipment maintenance,

The Walking Egg Charter

The Walking Egg npo is an international non-profit organization based in Genk, Belgium.
The Walking Egg believes that infertility care is a neglected aspect of family planning in resource-poor countries and therefore aims to raise global awareness about childlessness and infertility in developing countries.
The main goal is to make infertility care, including assisted reproductive technologies, available and accessible to a much larger part of the world population.
The Walking Egg has chosen for a multidisciplinary and global approach to realize the implementation of "accessible infertility services", the so-called ***Walking Egg Centres***.
Although the organization is made up mainly of doctors and health sector workers, it is also open to all other professions which might help in achieving its aims.

The Walking Egg Centres agree to honour the following **conditions**:

- Good quality family planning and mother care facilities are available. Ideally infertility management should be integrated into sexual and reproductive health care programmes
- An endoscopic surgery unit is available in the neighbourhood
- At least two dedicated specialists available (gynaecologist, embryologist)
- Training, quality control, regular audit and systems of accreditation and registration will be implemented in order to maintain appropriate standards of care
- To provide affordable infertility care according to the **philosophy** of The Walking Egg considering diagnostics, therapeutical procedures and data registration.

The Walking Egg Philosophy

The Walking Egg actions are guided by medical ethics, the principles of high quality medical care and accountability.

Medical ethics

We carry out our work with respect for the rules of medical ethics, in particular the duty to provide infertility care without causing harm to individuals or groups. We respect patients' autonomy, patient confidentiality and their right to informed consent. We treat our patients with dignity, and with respect for their cultural and religious beliefs. In accordance with these principles, TWE endeavours to provide high-quality medical care to all patients.

High quality medical care

Our decision to offer assistance in any country is based on an independent assessment of people's needs.
If assisted reproductive techniques, including intrauterine insemination and IVF can be offered, the TWE guidelines have to be followed:
Actions to prevent the most common complications of ART are obligatory

- Single embryo transfer (SET) recommended or double embryo transfer (DET) in selected cases to prevent multiple pregnancies
- The use of natural cycle / modified natural cycle protocols or mild ovarian stimulation protocols in IVF to prevent OHSS (ovarian hyperstimulation syndrome)

Using TWE materials for IVF
Only IVF due to the methodology of the simplified IVF system
Preferably childless couples
If HIV-positive: ART only performed if anti-HIV medication is freely available

Accountability

The Walking Egg is committed to regularly evaluating the effects of its activities. We assume the responsibility of accounting a strict follow-up of our Walking Egg Centres and to inform our donors on a regular basis.

Fig. 1. — The Charter and Philosophy of The Walking Egg Project

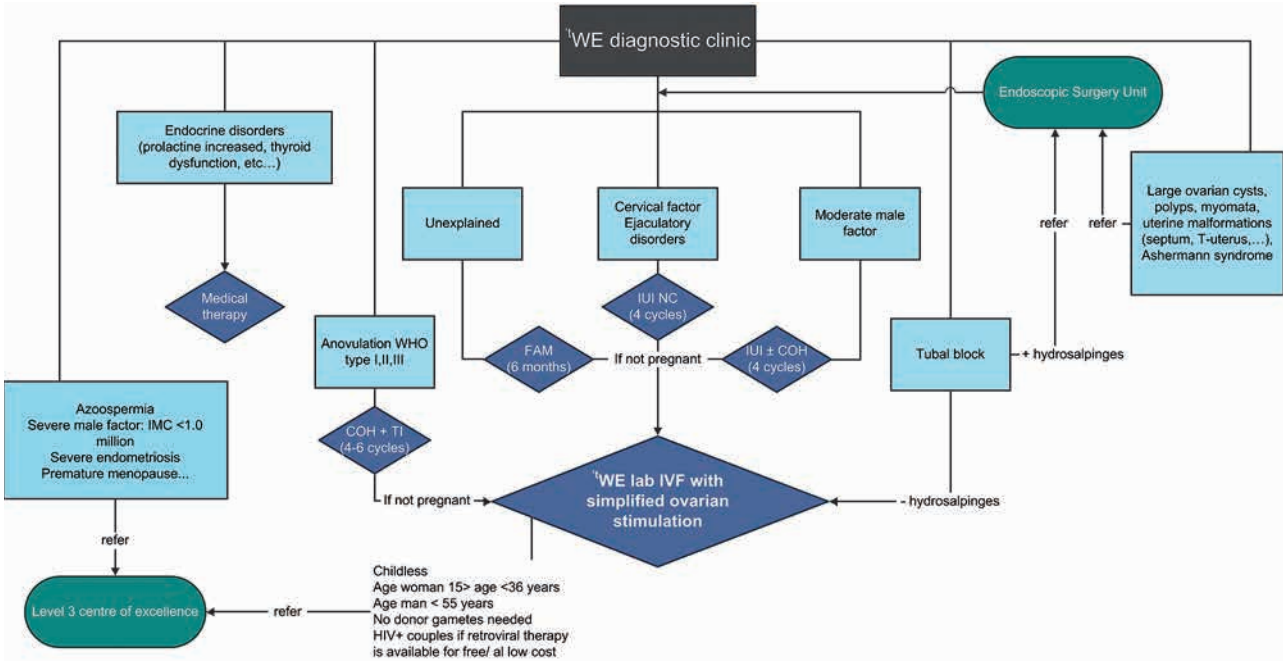

Fig. 2. — Proposed flowchart for the 'WE diagnostic clinic ('WE = the Walking Egg, FAM = Fertility Awareness Methods, IUI = Intrauterine insemination, NC = Natural cycle, COH = Controlled Ovarian Hyperstimulation, TI = Timed Intercourse, IMC = Inseminating Motile Count).

cost of investigations, cost of medical interventions and the cost of medication. Special servicing contracts should be negotiated with the manufacturers. In addition, simplification of the consumables should be taken into consideration and laboratory reagents and culture media should have a long shelf life. Special prices for medication should be negotiated with the drug manufacturers and simple treatment protocols should be put into action in order to reach the best cost-effective therapies.

5. ***Documentation and registration*:** We believe that within each pilot-centre on-line data registration of all ART activities is mandatory. Administrative staff and (para) medicals have to be aware of the importance of correct and trustable data registration. The ultimate goal is to offer all pilot-centres a similar registration programme, which should be customer-friendly with a limited but sufficient number of items (Ombelet et al., 2012). Continuous monitoring of service activities will be centralized, and provide feed-back to clinics for clinical and laboratory policy adjustments, information to couples on clinic performance, and information to society. Confidence can then be built and maintained.
6. ***Psychological and socio-cultural follow-up:*** When implementing low-cost (accessible) infertility services in DC it is extremely important to study social, psychological, sexual, legal and ethical aspects of infertility and infertility treatment and take study findings into account when setting up gender and cultural sensitive infertility services.

Selection of countries / pilot-centres

Decision making on infertility treatment in developing countries assumes answers to quite a few questions: How should the infertility problem be defined? How often does infertility occur? What is the income in that specific country and what to be spent on health care? How cheap should IVF be in order to be accessible to a considerable part of the population?

In this respect we believe that measurements of the (utility-measure oriented) Quality of Life over the infertile life-course in developing countries are urgently needed.

The selection of centres where the first pilot centres are implemented will be based on (1) available data on the resources, needs and resource gaps for infertility services on a national level, (2) percentage of GDP spent on education and health care, (3) the availability of endoscopic surgery facilities in the neighbourhood, (4) a good quality family planning unit, (5) good quality mother care facilities and (6) the availability of at least one experienced and dedicated gynaecologist and biologist (Fig. 1).

Potential TWE centres have to agree on the philosophy and the conditions of the Walking Egg Project as described in Figure 1. The one-stop

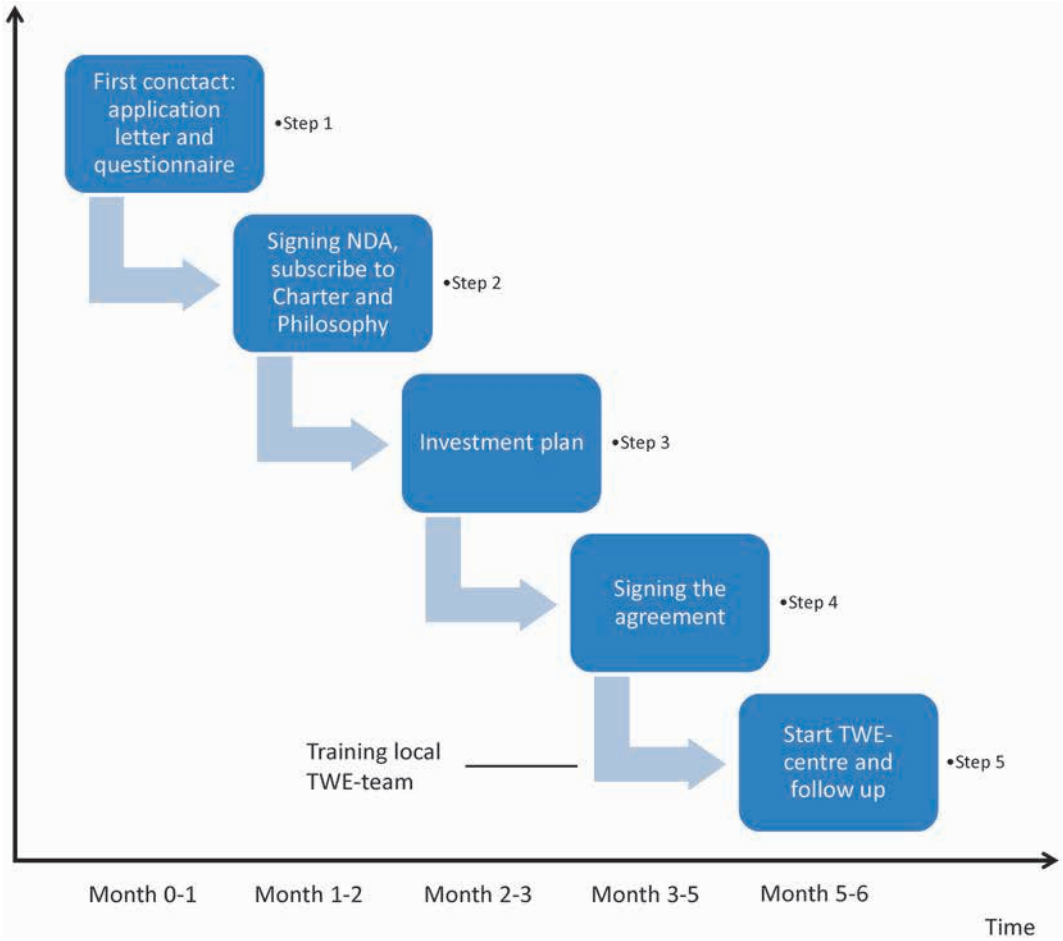

Fig. 3. — Different steps and time frame to become a Walking Egg centre

diagnostic phase with a **standardized investigation of the couple** at minimal costs will enhance the likelihood that infertile couples will come to the infertility centres. All the procedures of the one-day diagnostic clinic can be performed by a small team of health care providers within a short period of time in an inexpensive setting (Ombelet and Campo, 2007). A flowchart for the tWE (The Walking Egg) diagnostic clinic is shown in Figure 2. Future studies are planned to assess the reproducibility of 'one-stop infertility clinics' in different developing countries. Minimal (low-cost) ovarian stimulation protocols to avoid multiple pregnancies and severe medical complications such as ovarian hyper-stimulation syndrome (OHSS) are mandatory, not only in an IVF setting but also in IUI (intrauterine insemination) programmes. This strategy will drop the cost for assisted reproductive technologies significantly, especially when the simplified tWE IVF procedures are used (Ombelet et al., 2013; Ombelet and Campo, 2008; Van Blerkom et al., 2014).

Application to become a TWE centre

Every centre participating in the project accepts the rules and philosophy of the concept. This implicates also that a tWE-centre is by preference equipped by the tWE organization. In that way, tWE is also responsible for the validation, implementation and follow-up of the project.

There are 6 steps to be taken over a period of about 6 months, described in Table I and Figure 3.

Conclusion

We believe that the Walking Egg Project can change the attitude towards childlessness and infertility care substantially, not only in the developing world, but also in our Western countries. In developing countries, family planning and mother care should be integrated in the project. A high quality but affordable service delivery with special attention to the prevention of complications and unnecessary interventions has to become the trademark of this project. Adequate training and a strict follow-up of

Table I. — Detailed information about of the different steps to become a Walking Egg centre.

Step 1

First contact with an application letter where the interested centre motivates their interest.

We need to know specifications on:

→ The facilities

Space availability?
Is permanent water and electricity supply available or are there regularly discontinuances? Do you have a proper generator or water source?

→ Instruments

Detailed information about the already available equipment

→ Work environment:

Are they situated in a hospital?

Is there a special program on maternal care?

Do they have an endoscopic Unit?

Is there an IVF-centre in the neighbourhood?

→ Informatics (IT)

Does your centre have an integrated PC-system or more a stand-alone setup of PC's? Which program do you run?

→ Staff Members

CV (educational degree) of the persons who will be working for tWE-project.

If possible an organogram of the gynaecological-obstetric department.

→ Funding

How will the center be organized? Will it become a private, public or private/public organization?

Step 2

Once we have received the answers, we will send an ***NDA*** (non-disclosure agreement) and an invitation to ***subscribe to the Charter - Philosophy*** of the project. The NDA is **NOT** a contract but only a document to share all the necessary information with each other. If one agrees with the principles, both documents are signed and sent back to tWE- central office.

Step 3

Once the NDA and the Charter are signed we will send the ***scenario*** of the project. This scenario contains all necessary information on the project and will be the basis for a tailored roll-out and implementation of the local tWE-centre.

At this moment a prospection visit to your centre by tWE-team can be organized to speed up the implementation of the methodology.

Step 4

The next step is ***signing of the agreement***, which will also include a description of the tools that are delivered to your centre.

Step 5

Once the agreement is signed, the candidate-centre becomes a tWE-centre and they can ***start*** offering the tWE-treatment. The staff will receive special ***training*** by an experienced tWE-team. The training will be partly held in already existing tWE-centre and partly held on the location itself.

Step 6

Close follow-up on the medico-technical performances and the compliance with the tWE Philosophy will be done by tWE-staff members. In case of problems, the tWE-centre can ask for assistance of the tWE-staff, either on distance or on the spot. ***Regular audits*** are planned to ensure high quality standards.

the project are mandatory, public-private partnership may facilitate the development and implementation of Walking Egg centres and a positive relationship with and support of the local health care providers, politicians or other institutions should be stimulated.

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A Multicentre trial comparing the tWE lab laboratory system with standard IVF culture techniques

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Introduction

In our pursue to achieve the millennium development goals among others, the improvement of maternal health (United Nations Millennium Development Goals, 2008) in the form of reducing maternal deaths and providing comprehensive reproductive health service, global partnership for development should be considered one of the instrumental strategy.

Approximately 15% of couples worldwide (Boivin et al., 2007) suffer from childlessness with significant and at times catastrophic consequences (Dyer et al., 2004, 2005; Fathalla et al., 2006). Severe tubal damage and male infertility are common reasons for infertility in the developing countries as a result of sexually transmitted infections, septic miscarriages and/or puerperal sepsis (Adetoro and Ebomoyi, 1991; Ericksen and Brunette, 1996; Van Balen and Gerrits, 2001). Unfortunately these patients can only be managed by assisted reproduction technology such as IVF (Ombelet et al., 2008). Of major concern is the inaccessibility to these effective treatment options due to high costs and complex laboratory services.

There are 3 cost drivers in assisted reproductive programs. Ovulation induction, laboratory cost and personnel. For the service to be widely available and affordable the ovarian stimulation protocols have to be modified to milder forms to reduce the cost of medication needed and the risk of complications such as OHSS (Verberg et al., 2009). The laboratory set up also needs to be simplified.

Therefore the aim of the study is to compare the standard incubator IVF outcomes with the tWE Lab (Ombelet, 2014; Van Blerkom et al., 2014) IVF outcomes in a multicentre prospective randomised study.

Research question:

Is simplified embryo culture system as effective as standard incubator embryo culture system in IVF?

*Hypothesis***:**

Our hypothesis is that simplified tWElab embryo culture system may be as effective as standard incubator culture system in IVF.

Aims of the study:

Evaluate the effectiveness of tWE Lab embryo culture system versus standard incubator culture system in IVF.

Objectives of the study are:

Primary outcomes:

To evaluate the fertilization rates, clinical pregnancy rates (CPR), and on-going pregnancy rates (OPR) per cycle of tWE Lab embryo culture system versus standard incubator culture system in IVF.

Secondary outcomes:

To evaluate the total number of oocytes collected,
To evaluate the miscarriage rates,

Methods and Materials

Study Design: Randomized Controlled Multicentre Trial in Southern Africa.

Target Population: All patients with bilateral tubal occlusion, mild male infertility (1 million motile sperms after washing and three previously failed artificial inseminations (IUI)).

Study Population: All patients who require ART in the form of IVF.

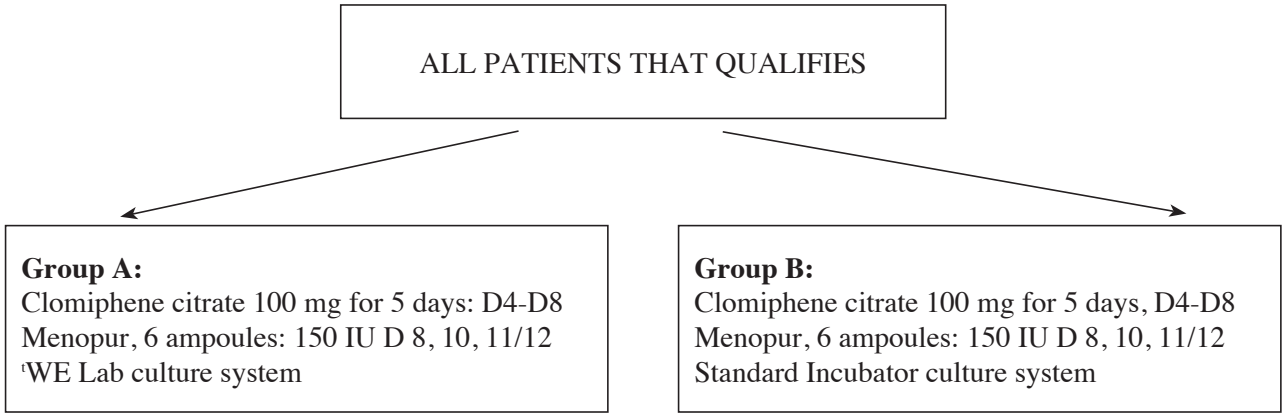
- *Setting:* The trial will be conducted at Tygerberg Hospital, Reproductive Medicine Unit, Aevitas Clinic Cape Town and 2 other centres to be recruited.
- *Inclusion criteria:* Female patients age between 18-37 years. It must be their first IVF treatment, with regular menstrual cycle (25-32 days) and a BMI (kg/m^2) of 18-29.
- *Exclusion criteria:* Female patients > 37 years. Patients with previously failed IVF treatment and the presence of large ovarian cyst of ≥ 3 cm on ultrasound were excluded. Patients with severe male infertility, moderate to severe endometriosis and vaginal and/or uterine abnormalities were also excluded.

Study sample: Consecutive patients who qualifies for ART in the form of IVF

Randomization method: Balanced block design following patient information assessment. No new patients will be enrolled once the sample size is reached.

Sample size: A statistical program (Epi-info, UMassAmherst) was used to do a sample size calculation for this study. Using given parameters-confidence (95%) and the power (80%) it was evident that using one hundred and seven per treatment group would be sufficient.

Data Source: The groups will be separated into two, Group A, minimal stimulation IVF with CC 100mg for 5 days and ≤ 6 ampoules of Menopur with tWE Lab culture system and Group B, minimal stimulation IVF with CC 100 mg for 5 days and ≤ 6 ampoules of MenopurIVF with standard incubator culture system.



Data collection and handling:

Patient information will be handled safely and confidentially. We will do double entry to ensure accurate collection.

Statistical processing:

Descriptive statistics: We will use Statistical Package for Social Sciences (SPSS) for overall analysis and specific tests for specific data. *Analytic statistics:* Outcomes will be analysed at the end of the trial.

Ethics and Permission:

Consent form will be signed by all participants before the study begins. There will be consent forms in English, Afrikaans, and Xhosa to accommodate predominant languages in the area. Interviews and questionnaires will be administered on one by one basis to ensure patient's privacy and confidentiality. The drugs used in this trial are registered and used according to the manufacturer's recommendations.

This protocol forms part of the approved PhD study by the Faculty of Health Sciences at Stellenbosch University ethics committee meeting: *N11/08/256 but permission must be obtained for this new protocol*

Results: to be obtained

Conclusion and Discussion: We anticipate favourable outcomes with the tWe Lab culture system.

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Addendum

All patients will have a pre treatment ovarian assessment using antral follicle count, AFC.

Ultrasound will be done between the cycle day 1 and cycle day 3 thereafter on cycle day 8 and repeated every other day or daily for follicle tracking and endometrial thickness assessment. Urine sample will be taken for assessment of LH on the days the ultrasound. Ovulation trigger will be performed with subcutaneous injection of Ovitrelle® when a lead follicle has atleast 18 mm diameters. Transvaginal ultrasound-guided follicle aspiration will be performed 34-36 hours after the hCG administration.

Generally embryo transfer will be performed on the third day after oocyte retrieval for both groups. Luteal phase will be supported with vaginal progesterone from the day of embryo transfer until the day of pregnancy test.

Implantation is defined by positive pregnancy test, serum b-hCG ≥ 25 IU on the tenth day following embryo transfer. Clinical pregnancy is defined as the ultrasound presence of foetal cardiac activity at 7 weeks gestation and on-going pregnancy is defined as the presence of a foetus of > 12 weeks on ultrasound.

The cycle will be cancelled if < 2 dominant follicles are present and the LH > 20IU/L and there are no quality embryos to transfer.