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Keep it simple: specific aspects of IUI in developing countries

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Introduction

Assisted reproduction (ART) is now an established therapy for the treatment of infertility in a multitude of clinical conditions. It embraces a wide scope of techniques including intrauterine insemination (IUI), in-vitro fertilization (IVF), gamete intra-fallopian transfer (GIFT), zygote intra-fallopian transfer (ZIFT) as well as intra-cytoplasmic sperm injection (ICSI). It is estimated that more than 3 million babies have now been born from ART. However, the great majority of those babies were born to couples living in developed countries (Ombelet, 2008; Ombelet *et al.*, 2008a). Various attempts are now being made to adapt these techniques for use in developing countries and bring this technology to the less fortunate (Sallam, 2008). This paper will discuss the specific aspects of one of these techniques, namely IUI, as it relates to developing countries and various methods to simplify it to maximize its benefits in these countries.

Developing countries

Two definitions of developing countries are currently being used: the World Bank definition and the United Nations Development Programme (UNDP) definition. The World Bank classifies countries according to their gross national income (GNI) per capita into low income, middle income (subdivided into lower middle and upper middle), or high income countries. Low income countries are those with a GNI of US$ 905 or less, lower middle income with a GNI of US$ 906-3595, upper middle income with a GNI of US$ 3596-11115, while high income countries are those with a GNI of US$ 11116 or more. Low income and middle income countries are sometimes referred to as developing countries. Although the use of the term is convenient for financial purposes, it does not necessarily reflect the development status of the country in question (Sallam, 2008).

Consequently, other measures for the classification of developing countries have been used by other international agencies. The UNDP takes into consideration three criteria for the evaluation of countries' development: the low income criterion, the human resources weakness criterion and the economic vulnerability criterion. Based on these criteria, the UNDP has compiled a list of the 50 least developed countries (LDC). Of these 34 are in Africa (Sallam, 2008).

Specific aspects of infertility in developing countries

Infertility in developing countries has its specific aspects and differs from infertility in the developed world in many ways. These include differences in its prevalence, its causes, the role played by infection as well as its effects and consequences. In addition, culture plays an important role in the causation, diagnosis and management of infertility in developing countries and scanty financial resources is an ever present factor affecting the provision of fertility services to these less fortunate patients.

Widespread differences exist in the prevalence of infertility in developing countries. In a study by Boivin *et al.*, the prevalence of infertility ranged from 3% of married couples in Shanghai in China to 25.7% in Chile (Boivin *et al.*, 2007). This confirms earlier findings that the prevalence of secondary infertility was 16% in North Africa, 23% in Asia, 40% in Latin America and 52% in Sub-Saharan Africa (Cates *et al.*, 1985). In Africa, Ericksen and Brunette found that the average prevalence for the whole continent was 14.9%, ranging from 9.8-12.2% in Eastern Africa to 16.7-21.4% in Southern Africa (Ericksen and Brunette, 1996).

There is also widespread variability in the causes of infertility in developing countries. In the study by Cates *et al.*, infertility was due to female causes in 25 to 37% and to male causes in 8 to 22% of couples. Both male and female causes were present in 21 to 38% of the couples. This variability has been blamed on various factors including variability in the sexually transmitted, infectious, and parasitic diseases, health care practices and policies as well as exposure to potentially toxic substances in the diet or the environment (Cates *et al.*, 1985). In particular, infection plays a disproportionately higher role in the causation of infertility in developing countries including gonorrhoea, Chlamydia and HIV (Ombelet *et al.*, 2008a).

In addition, infertility has serious effects on the life of women in developing countries including their social standing and psychological health. These effects include loss of social status, social isolation, marital instability, loss of social security, negative effects on gender identity as well as psychological consequences (guilt, depression, shame, grief and/or sense of worthlessness). In some communities, the stigma of infertility leads to violence against women (Ameh *et al.*, 2007). In some communities, it may even follow them to their graves, where traditional funeral services may be denied to them as they are considered witches or bringers of bad luck (Araoye, 2003; Ombelet *et al.*, 2008a). Other cultural factors affecting infertility in developing countries include the culture of son-preference, the bias against gamete donation and treatment of non-traditional families (Sen, 2003).

On top of these burdens, many obstacles to treating infertility in developing countries exist. These include lack of services, lack of know how, lack of access to services, acceptance of fate (curse from God), bad experience of neighbours, resorting to traditional healers as well as lack of finance (Nygren and Zegers-Hochschild, 2008). In fact developing countries, which form 84% of the global population and carry 90% of the global burden of disease, spend 12% of the global health spending compared to 88% spent by developed countries which form 16% of the world population and carry 10% of the global disease burden. In addition the public share of the total health spending is 29% in developing countries compared to 65% in developed countries (Schieber and Maeda, 1999).

Specific aspects of IUI in developing countries

IUI is the simpliest form of assisted reproduction and offers particular advantages to developing countries as the first line of ART management. These include the minimal equipment required, an easy technique to learn, being less invasive, less expensive with a reduced psychological burden on the couple. In addition, IUI has a good couple compliancy (low dropout rate), a low risk for OHSS and a low multiple pregnancy rate with natural cycles, clomiphene or low-dose HMG protocols (Ombelet *et al.*, 2008b).

However, in order to maximize the benefits of IUI in developing countries, some modifications have been suggested in order to render the technique cost effective under the circumstances of these countries. These include the use of simple stimulation protocols, simple monitoring techniques for timing IUI, simple methods for the evaluation of the semen sample, the use of simple sperm preparation techniques, simple insemination devices, simple insemination techniques and special precautions relating to HIV contamination.

1. Simple stimulation protocols

Various studies have shown that performing IUI with ovarian stimulation increases the pregnancy rates significantly compared to IUI in non-stimulated cycles. In a meta-analysis by Hughes, the odds ratio (OR) for clinical pregnancy in stimulated cycles versus non-stimulated cycles was 2.37 with 95% confidence interval (CI) of 1.43 to 3.90 (Hughes, 1997).

The success rate of IUI is also a function of the number of follicles developing in response to stimulation. In a recent meta-analysis by van Rumstke *et al.*, the absolute pregnancy rate was 8.4% for monofollicular and 15% for multifollicular growth. The pooled OR for pregnancy after two follicles as compared with monofollicular growth was 1.6 (99% CI = 1.3-2.0), whereas for three and four follicles, this was 2.0 and 2.0, respectively. However, the risk of multiple pregnancy increases also with the number of follicles. The pooled OR for multiple pregnancies after two follicles was 1.7 (99% CI = 0.8-3.6), whereas for three and four follicles this was 2.8 and 2.3, respectively (van Rumstke *et al.*, 2008).

Consequently, most infertility specialists perform IUI in stimulated cycles and it has generally been assumed that HMG stimulation can lead to higher pregnancy rates compared to clomiphene citrate (CC). In another non-controlled study on IUI in CC/HMG stimulated cycles, the clinical pregnancy rate was 12.6% per cycle and the multiple pregnancy rate was 13.7% (Nuojua-Huttunen *et al.*, 1999).

However, in a study by Ombelet *et al.* (1997), patients treated with CC and IUI (without HMG) achieved similar results with an overall cycle fecundity (CF) and baby take-home rate (BTH) of 14.6% and 9.9% respectively. The cumulative CF and BTH (per couple) after three cycles were 30.6% and

21.1% respectively. These findings were similar in all patients except when the insemination motile count was $< 1 \times 10^6$ with a morphology score of < 4% normal forms. There were only two twin pregnancies (2.5%) and no moderate or severe OHSS. These findings were confirmed in a cross-over study by Ecochard *et al.* (2000) who compared CC to HMG stimulation in IUI cycles and found no significant difference in clinical pregnancy rates between both regimens.

More recently, Dhaliwal *et al.* (2002) compared the conventional CC + HMG daily (from day 8) protocol to a minimal stimulation protocol of CC + one HMG injection (150 IU on day 9) in patients undergoing IUI. They found no significant difference in clinical pregnancy rate per cycle (19.12% versus 16.20%) between both regimens. The risk of miscarriage was significantly lower with minimal stimulation (5.7% versus 23%; $P < 0.05$). The multiple pregnancy rate was 5.13% and the incidence of OHSS was 3% in the conventional stimulation protocol versus none in the minimal stimulation protocol (Dhaliwal *et al.*, 2002). More importantly, the cost of the treatment cycle was US$ 63.50 for the minimal stimulation cycle versus US$ 216.50 in the conventional stimulation cycle. It is therefore clear that CC stimulation prior to IUI can be used safely and effectively in settings with low resources such as developing countries.

2. Simple monitoring techniques and timing of IUI

Various methods for monitoring ovarian stimulation and timing IUI have been proposed. These are based on the probabilities of conception models developed by various groups (Barrett and Marshall, 1969; Schwartz, 1980; Royston, 1982).

In 1982, we used serial ultrasound monitoring of folliculogenesis and performed the insemination when the leading follicle reached 18 mm in diameter. Using this technique we achieved a 12% pregnancy rate ?CF versus 6% in patients monitored with basal body temperature charts (Marinho *et al.*, 1982).

Subsequently, two other methods were used for timing IUI, namely serial measurement of urinary LH and triggering ovulation by the IM injection of 5000 – 10000 IU of HCG, with various claims of success. In 2007, Kosmas *et al.* performed a meta-analysis of seven prospective and retrospective studies and found that patients who received hCG before IUI demonstrated lower clinical-pregnancy rates than did women who had IUI after spontaneous ovulation (OR = 0.74; 95% CI = 0.57 to 0.96) (Kosmas *et al.*, 2007). In another study, there was no difference in clinical pregnancy rates when insemination was performed once at 24 hours or twice at 12 and 36 hours after HCG administration (Tonguc *et al.*, 2009).

Other methods for timing IUI have been proposed including the serial measurement of serum or salivary oestradiol or its metabolites (oestrone-3-glucuronide, oestradiol-16alpha-glucuronide and oestriol-16beta-glucuronide) in urine or in saliva (Branch *et al.*, 1982; Sallam, 1983; Tanabe *et al.*, 2001). However, these are more expensive and are only commercially available in some developed countries. Consequently, in a low resources setting, timing IUI with the use of relatively expensive and time-consuming methods does not increase the pregnancy rate over folliculometry or urinary LH monitoring of ovulation (Zreik *et al.*, 1999).

3. Evaluation of the semen sample

Traditionally, the evaluation of the semen sample consisted of the measurement of its volume, count, percentage of motile spermatozoa, of abnormal forms and an estimate of the white blood cells per high power field. Subsequently, evaluation of sperm morphology using strict criteria was introduced (Kruger *et al.*, 1987) as well as computer-assisted semen analysis to measure more sophisticated indices of sperm motility (Holt *et al.*, 1985; Vantman *et al.*, 1988). In addition a number of sperm function tests have been described with various claims of their efficiency in determining the fertilizing capacity of the sperm (Aitken, 2006).

In an attempt to determine the relative importance of the various criteria used in semen evaluation, we analyzed 11 sperm parameters, namely sperm count, eight sperm velocity parameters determined by computer-assisted semen analysis, sperm morphology score using strict criteria and the hypo-osmotic swelling (HOS) test. Data from 58 couples treated with IVF were analyzed retrospectively by simple linear regression and multiple stepwise regression analysis, taking the fertilization rate as the dependent factor. The mean sperm velocity and the strict sperm morphology assessment were the only parameters showing significant correlation with the fertilization rate. A minimum sperm velocity of 13 μm/sec and a minimum strict sperm morphology percentage of 2% were necessary to achieve fertilization in 50% of the oocytes. The results of the HOS test did not correlate with the fertilization rate (Sallam *et al.*, 2003). These results confirmed the earlier work by Menkveld *et al.* (2001) who, using ROC curves, reported cut-off values of 8% for the acrosome index, 45% for motility, and 4% normal spermatozoa for strict criteria.

Consequently, proper evaluation of the semen sample can be achieved by the simple but accurate determination of the sperm count, sperm motility and sperm morphology using strict criteria, as resorting to complicated and more expensive semen evaluation techniques is not necessary for the majority of infertile couples. Training courses for laboratory technicians on semen evaluation are conducted regularly with help of WHO in various parts of the world in order to standardize the procedure and many of these courses are conducted in developing countries, particularly in Africa (Franken and Aneck-Hahn, 2008).

4. Simple sperm preparation techniques

Various sperm preparation techniques for IUI have been described. The most commonly used are sperm washing and centrifugation, the swim-up method as well as centrifugation on discontinuous Percoll, Ficoll or Nycodenz gradients (Gellert-Mortimer *et al.*, 1988; Bongso *et al.*, 1989; Van der Zwalmen *et al.*, 1991). Other less commonly used methods are glass bead column, swim-down, and sperm select systems (Fahmy, 2005).

A recent meta-analysis was conducted by Boomsma et al. Five RCTs, including 262 couples in total, were included in the meta-analysis. The reviewers found that no trials reported the primary outcome of live birth. There was no evidence of a difference between pregnancy rates (PR) for swim-up versus a gradient or wash and centrifugation technique (OR = 1.57, 95% CI = 0.74 to 3.32; OR = 0.41, 95% CI = 0.15 to 1.10, respectively), nor in the two studies comparing a gradient technique versus wash and centrifugation (OR = 1.76, 95% CI = 0.57 to 5.44). There was no evidence of a difference in the miscarriage rate (MR) in two studies comparing swim-up versus a gradient technique (OR = 0.13, 95% CI = 0.01 to 1.33) (Boomsma *et al.*, 2007). In summary, no method proved its superiority over the others.

Consequently, in low resource settings such as in developing countries, the simplest sperm preparation technique should be used. The swim-up method can therefore be used when the sperm count is adequate (> 5 million/ml), while the wash and centrifugation can be used when the count is low (< 5 million/ml). Gradient techniques should be reserved for infected samples.

5. Simple insemination devices

Different catheters have been used for IUI with various claims of success. It has been suggested that soft catheters may be less traumatic to the uterine cervix or to the endometirum. However, in a study by Miller *et al.* (2005), who compared the more rigid but cheaper Tomcat catheter to the softer and more expensive Cook catheter, there were no significant differences in clinical pregnancies between both catheters. These findings were later confirmed in a meta-analysis showing no significant differences in clinical pregnancy rate and live birth rate between both groups (OR = 0.96; 95% CI = 0.70 to 1.32 and OR = 0.82; 95% CI = 0.43 to 1.58, respectively) (Abou-Setta *et al.*, 2006).

6. Single versus double insemination

It has been suggested by different groups that performing IUI on two occasions during the same cycle may increase the chances of pregnancy. However, in a recent meta-analysis, involving 829 women from 6 randomized trials, there was no significant difference between the single and double IUI groups in the probability of clinical pregnancy (OR = 0.92; 95% CI = 0.58 to 1.45). The mean fecundity rate was 13.6% for double inseminations versus 14.4% for single inseminations (Polyzos *et al.*, 2009). This confirms the findings in an earlier Cochrane review which concluded that double intrauterine insemination showed no significant benefit over single intrauterine insemination (OR = 1.45; 95% = CI 0.78 to 2.70) (Cantineau *et al.*, 2003).

7. IUI in the presence of chronic viral diseases including HIV/AIDS

IUI for patients infected with chronic viral diseases presents a real challenge to the personnel involved in their treatment. HIV is endemic in many developing countries in Africa and Asia as is HBV and HCV. These viruses and others can be transmitted by IUI and present a health risk to the personnel dealing with the infected semen samples. Cross-contamination in tanks storing frozen semen samples is another hazard.

However, it has now been established that methods of preparing the sperm in which the seminal plasma is removed by washing and sperm are separated from the other cellular elements of the sperm (e.g. centrifugation on discontinuous gradients) can reduce the viral load up to an undetectable level (Semprini and Fiore, 2004). In a study by Bujan *et al.* (2007) 84 HIV-1 serodicordant couples underwent 294 IUIs. Spermatozoa from HIV-1 infected male partner were prepared and tested for HIV-1 using the sperm washing method. The pregnancy rate per cycle and baby take-home rate per couple were 18.0% and 52.4%, respectively. No female HIV-1 contamination occurred.

It has also been suggested that the systematic use of ICSI is the treatment of choice in these cases. In a recent study by Sauer *et al.*, 420 ICSI cycles were performed in 181 HIV sero-discordant couples where the man was carrying the virus. The clinical and ongoing pregnancy rates per embryo transfer were 45% and 37%, respectively. No maternal or neonatal HIV infections or deaths occurred. In an attempt to further minimize the risks, Englert *et al.* (2004), suggested to perform systematic screening before IUI, to have a separate "infected laboratory", to adapt a set of safety procedures and to do HIV testing post preparation. The implementation of the latter policies in developing countries is obviously impractical.

Conclusions

IUI is a simple, affordable and effective treatment for infertility in indicated cases and is particularly suited to developing countries. Randomized trials have shown that IUI can be successfully performed in patients with limited resources using simple approaches. In those patients, clomiphne citrate stimulation should be prescribed and insemination timed with urinary LH monitoring or serial ultrasound folliculometry. The swim up technique should be used when the semen count is adequate and washing and centrifugation if the count is low. Gradient separation should be reserved for patients with pyospermia or virus infection. Rigid cheap catheters perform as well as softer and more expensive catheter, one insemination is as good as two and special strict precautions should be taken in communities with a high incidence of HIV/AIDS.

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