‘Slow release intrauterine Insemination als neue Methode der IUI’ by Maximilian Franz und Julian Marschalek

‘Gyne’ – Fachzeitschrift für den Arzt der Frauen Edition 7-8/2014 (Translation B. Watkinson/ Approved J. Marschalek)

‘Slow release intrauterine Insemination as a new methode of IUI’ by Maximilian Franz und Julian Marschalek

Improving the success rate of IUI is a concern that countless studies shared in the past. Slow Release Intrauterine Insemination (SRI) as a new method of IUI gives new hope. First study results show that SRI may improve pregnancy rates.

In cases of idiopathic sterility, endometriosis grade I-II and mild male subfertility, intrauterine insemination (IUI) is still the first choice of fertility treatment. Further fields of application range from donor insemination to erectile dysfunction or couples with other forms of sexual dysfunction. With 1.5 – 2.5 million cycles carried out globally annually, IUI is without any doubt the most commonly applied method; a fact certainly also resulting from IUI being the least invasive and least expensive infertility treatment.

Pregnancy success rates following IUI, however, are still unsatisfactory and according to published scientific literature, depending on age and concomitant medication, are between 5 – 15%. An analysis of data by the European IVF-Register 2004, which evaluated almost 100.000 insemination cycles, shows a birth rate of 12.3% across all cycles [1]. According to a large retrospective study from the Netherlands with more than 15,000 evaluated IUI cycles, the pregnancy rate per cycle is 6.5%. Three, seven and nine cycles demonstrated a cumulative pregnancy rate of 18%, 30% and 41%. [2]

Andrological factors

To date there are no definite minimum criteria regarding sperm analysis leading to successful IUI. Amongst the different parameters, the Total Motile Sperm Count (TMSC) - total number of post-washed moving sperm – appears to be the most reliable prognostic parameter. Several studies [3,4] show that TMSC should be at least 5 million and that a successful insemination with lower values is unlikely.

A TMSC of more than 10 million has not shown any improvement in pregnancy rates [5]. Up until recently an abstinence of 3 to 5 days prior to IUI was advised in order to achieve maximum sperm density and TMSC. Latest data however, show the highest pregnancy rates with an abstinence of only three or even two days.

Improving the success rate of IUI is a concern that countless studies shared in the past

The improvement of pregnancy rates in recent years is mainly due to the modification in sperm preparation. Many studies concentrate on evaluating different stimulation protocols and ovulation induction, whereas the method of IUI remained mainly unchanged [7-9].

A Cochrane Review from 2012 concluded that the live birth rate in couples with unexplained infertility is higher after IUI with controlled ovarian hyper stimulation than IUI alone. A Cochrane analysis of six prospective studies with over 500 patients showed that IUI is 1.6 times more successful in stimulated cycles compared to monitored cycles [10]. The analysis also revealed that inseminations during stimulated cycles increased pregnancy rates compared to IUI during a natural spontaneous cycle.

Which stimulation protocol is best?

Berker at al. demonstrated that clinical pregnancy rates may be increased via stimulation with recombinant FSH (rFSH) compared to Clomiphen (15.6% vs 9.6%, p=0.31). However, due to the small amount of cases (189 cycles) significance could not be demonstrated.

The use of GnRH antagonists to prevent premature ovulation was also evaluated in several studies. In 2012, two highly publicised studies lead to controversial results. In an open label study, pregnancy rates were significantly improved by combining GnRH antagonists with rFSH [12], whereas a much larger double blind study showed no difference in pregnancy rates and live birth rates (Placebo 12%, GnRH n8.4%, p=0.3)[13].

Another frequently asked question is that of ovulation induction vs endogenous LH increase prior to IUI. Most studies describe the point of insemination of 32 – 36 hours after administration of hCG or 24 hours following the endogenous LH surge. A Cochrane meta-analysis from 2012 did not find a significant difference with regard to live birth rates and the above mentioned timing methods in IUI. Nevertheless, the data is inconclusive, so there cannot be a general recommendation for either process.

Few studies so far have questioned or modified the technical aspects of IUI

Initial approaches to modify the technical aspects of IUI were made in the early 1990s with 'Fallopian Tube Sperm Perfusion' (FSP). This method was primarily used in women with non-tubal sterility. It is now, however, evident that FSP is not necessarily superior to IUI [15]. The first study of Slow-Release-Insemination (SRI) was carried out in1992 by Muharib et al, during which insemination was carried out over a period of three hours [16]. This improved pregnancy rates per cycle from 6.1% to 15.0% ($p<0,005$) and increased the cumulative pregnancy rate significantly after four cycles from 22% to 63.1% ($p<0.05$). Still, statistical power was weak with only 126 cycles carried out. The idea of improving the chance of fertilisation by slowly introducing sperm into the uterus is based on several theories: The slow and continuous discharge increases the time of potential contact between sperm and egg and the chances of sperm flowing back into the vagina or their discharge via the tubes into the abdomen are decreased. In addition, a sperm bolus resulting in possible polyspermia or triggering an immune reaction can be avoided.

In order to closer investigate the approach of SRI, a randomised multicentre study in cross-over design was launched in 2012. During this study each patient was either treated with one SRI and in case this did not lead to a pregnancy this was followed by IUI or vice versa.

During SRI, a pump (Evie, ill.1) continually discharges 1.0ml of semen over a period of four hours via a balloon catheter into the uterine cavity. As the pump is small and lightweight, it is possible to strap it onto the thigh with a belt and the woman can go home once the pump is fitted. After the four hours have elapsed, the woman can remove the balloon catheter herself. In contrast, traditional IUI consists of a single bolus of 0.5ml.

The inclusion and exclusion criteria are listed in ill. 2. Here, the assessment of the spermiogram with a minimum of 10 million motile sperm per millilitre and more than 50% progressive motile sperm in preparation is particularly noticeable. Bearing in mind the above mentioned discussion [3-6] regarding the andrological factor, an increased pregnancy rate cannot be expected from the andrological inclusion criteria.

Initial and, as yet, unpublished data of this study concur with previous results and give rise to hope that SRI can increase pregnancy rates after IUI. 94 cycles were carried out in women under 35, which increased pregnancy success rates using Evie by a factor of 2.2x. However, due to the number of cases, this increase is not (yet) statistically significant (ill.3).

The average age of patients was 34.4. For the best centre in the study there is an increase from 13% (IUI) to 26.3% (SRI n.s.) across all age groups (ill.4) (including age over 35 women).

These figures must be interpreted with care and be assessed with the consideration that so far 94 cycles have been evaluated and that the current enrolment comprises 154 out of 250 planned cycles.

Still, it is evident that this is a new and promising approach, which might result in further progress in insemination methods.

Inclusion criteria

- Women with primary or secondary infertility after 6 months of unprotected sexual Intercourse, who qualify for IUI
- Age of the woman – 20 – 40 years
- Normal x-ray of the uterine cavity (HSG) or Chromopertubation to determine tubal patency
- Women with infertility due to lack of ovulation
- Infertility due to problems associated with the man (more than 10 million motile sperm cells per ml of sample and 50% progressive motile sperm in the preparation)
- Unexplained infertility
- Homosexual or single patient
- Signed declaration of consent

Exclusion criteria

- Age of the woman below 20 or above 40 years
- Infertility of the woman due to mechanical issues concerning the uterus or the fallopian tubes
- Infertility of the man due to medium or low number of spermatozoon – less than 10million motile sperm cells per ml of sample and 50% progressive motile sperm in the preparation
- Men and women who do not consent to the randomised insemination method
- Participants who do not sign the declaration of consent
- BMI >30

Ill.2: Inclusion and exclusion criteria of the SRI study