Clinical Outcome in Intrauterine Insemination Treatment of Sub-fertile Patients in the Teaching Assistance Reproductive Technology Centre, Albayda, Libya- A prospective Study

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Abstract

Controlled ovarian hyperstimulation (COH) and intrauterine insemination (IUI) are commonly used to treat sub fertile couples. In this study, the clinical outcome of COH and IUI was evaluated. 116 COH+IUI cycles were conducted for eligible couples who referred to Assistance Reproductive Technology (ART) Teaching Centre, Albayda-Libya. The primary outcome: clinical pregnancy and live birth rates. Clomiphene citrate or Letrozole were administrated orally for 5 days, starting on cycle day 2. Gonadotropin injections were given daily starting on cycle day 3 for 6-7 days. Serial ultrasound scanning was done to evaluate the patient’s response and the dose modified accordingly. When at least 2 follicles reached a size of ≥17mm, a trigger dose of 5000 or 10000 IU/ml hCG was given to induce ovulation. 34-36 hours later, prepared semen has been injected intrauterine. Serum β-hCG test was performed for women who experienced missed period. Ultrasonography performed at 7 week gestation for those with positive pregnancy test for evaluation of fetal cardiac activity. Result: Out of 116 IUI cycles, 103 IUI cycles were completed and analyzed, while 13 cycles were cancelled, cancellation rate was 11.2%. The overall clinical pregnancy rate was 15.5% with live birth rate of 8%. The miscarriage rate was 5.8%. The rate of ectopic pregnancy was 0.9% and one mother gave birth to triplet. No ovarian hyperstimulation syndrome (OHSS) was recorded. Conclusion: this study achieved a success rate comparable to other studies without increase in the incidence of multiple gestation or ovarian hyperstimulation Syndrome.

Keywords: subfertility; COH; IUI; pregnancy; live birth; ART.
Introduction

Subfertility is defined as failure to conceive after a period of at least 12 months of regular unprotected sexual intercourse [1]. According to the recent national estimates, subfertility affects 6% [2] to 15.5% [3] of couples. Subfertility can result from disorders in the female partner alone (25-30%), in the male partner alone (20%) or disorders in both (40%), in 10-15% of couples no cause could be found [4-5].

Different fertility treatment modalities are available; expectant treatment (lifestyle changes and timed intercourse), ovarian stimulation with either clomiphene citrate (CC), gonadotropins or combined CC and gonadotropins. Ovarian stimulation followed by intrauterine insemination (IUI), in-vitro fertilization (IVF) or Intra cytoplasmic sperm injection (ICSI). However, the choice of the most optimal treatment regimen for a subfertile couple can be confusing.

Ovarian stimulation in already ovulating women may overcome undiagnosed ovulatory problems because of limitation of the available tests; also it improves the cohort of growing follicles with subsequent increase in fertilization and gestational rate.

During IUI procedure, prepared semen sample inseminated directly into the uterine cavity thus by passing any undiagnosed cervical factor and increasing the concentration of motile sperms near the fallopian tube.

IUI may be recommended as a first-line management of infertile couples with different etiologies such as ovulatory disorders, male factor infertility or unexplained infertility [6]. In comparison to in-vitro fertilization-embryo transfer (IVF-ET), controlled ovarian hyperstimulation (COH) and IUI is a less expensive and less invasive treatment [7]. Thus combined ovarian stimulation with IUI has been found has been found to be the most practical treatment before moving on IVF. The success rate of COH+IUI varies between and 22% [8-10].

In our unit COH/IUI is the first-line treatment for sub fertile couples without tubal factor or severe male factor, therefore, the clinical outcome of a combination of COH and IUI for the treatment of infertility has been evaluated in the current study. Further work to be done to find the prognostic factors in treating infertile couples with COH and IUI and this would be helpful for the couples and clinicians to reasonably predict how successful the COH and IUI treatment.

Material and Method

The present study was designed as a prospective study and conducted in the Teaching Assisted Reproduction Technology Centre (ART) in Albayda-Libya from 8/2015 until 8/2016.

Study population

All couples had attempted to conceive for at least one year prior to undergoing COH and IUI, those aged >35 years were included in the study with infertility duration <1 year. After examining the infertile couples and gathering all infertility-related history of patients, both partners had undergone extensive evaluation according to basic infertility workup [11]. Examinations included at least two semen analyses; semen parameters were interpreted using the World Health Organization (2010) criteria [12]. The women underwent baseline (cycle day 2-3) pelvic ultrasound examination and hormonal level evaluation; follicular stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), thyroid-stimulating hormone (TSH), prolactin. Anti-Mullerian hormone (AMH) was done for patients older than 37 years. Hysterosalpingogram (HSG) and/or laparoscopy were used for tubal patency assessment.

Inclusion and exclusion criteria

Patients who met the following criteria were eligible for inclusion in the study: (1) mild male sub-fertility (2) male with dysfunctional problems like impotence (3) female partner with normal pelvic ultrasound scan, normal hormonal assay with
basal FSH ≤12 ng/ml (4) polycystic ovarian syndrome (PCOS) (5) endometriosis (6) unexplained infertility (6) at least one patent fallopian tube is mandatory. Exclusion criteria were: (1) patients who had clinically significant systemic or endocrine disorders (2) those with a diagnosis of any space-occupying lesion during HSG or hysteroscopy evaluation such as endometrial polyp, submucous myoma or uterine septum.

**Ovulation stimulation and follow up**

Patients who were eligible for inclusion in the study received either oral clomiphene citrate (CC) (100 to 200 mg daily) or letrozole (LTZ) (2.5 mg or 5 mg daily) for 5 days starting on cycle day 2. Letrozole mainly used for patients with PCOS. Gonadotropin injections (GnH) (manufacturer: IBSA) were given intramuscular daily starting on cycle day 3 and the dose was modified according to the response of the patient. Follicular development and endometrial thickness were assessed by serial transvaginal ultrasound ± hormonal assay. If the endometrial thickness was <7 mm, oral estradiol 2 mg/per day and/or per-vaginal Viagra tablet was administered and continued during the luteal phase. When at least 2 follicles reached ≥ 17 mm in diameter, intramuscular injection of 5000 or 10000 IU of human chorionic gonadotropin (hCG) (manufacturer Merck sharp& Dohme Limited) was given to induce ovulation.

**Cycle cancellation**

Indications for cancellation of the cycle: (1) poor response for COH (2) if the patient was at high risk to develop ovarian hyperstimulation syndrome (OHSS); large number of follicles ≥17 mm in size developed, or serum estradiol on day of trigger dose > 3000ng/ml.

**Semen collection and preparation**

Semen obtained by masturbation in a collection room adjacent to the laboratory after 3 days abstinence. Freshly ejaculated semen samples were microscopically examined to determine sperm motility and concentration after 30 minutes of liquefaction at room temperature (pre- preparation semen parameters).

In this study, the standard swim-up technique was used for semen preparation. Liquefaction of the seminal sample with buffer solution (G-MOPsT vitrolife) was performed in a sterile tube and centrifuged slowly at 1000–1500 rpm= g Force 1.350- 2.454 and the supernatant was discarded. This step was repeated 1-2 times and the remaining sperms were over layered with 1 cc of culture medium (G-GAMATE vitrolife)and stored inside an incubator at 37oC for 30- 60 minutes to cause sperms with the most motility to migrate to supernatant in order to be used for IUI. Sperm count and motility was calculated by an andrologist who was expertise in this area using the swim-up sample. All pre and post preparation semen parameters were recorded for patients shown in Table1. IUI procedure 34-36 hours after hCG injection, 0.7 ml of prepared semen sample was inseminated Intrauterine using an IUI injection catheter. The catheter was entered in the cervical orifice and driven directly into the uterine cavity. According to the protocol, the patients remained supine for 15 minutes. All participants were educated about prohibition of intercourse and NSAIDs use for 72 hours before and until 72 hours after the IUI.

**Patient follow-up**

A serum β-hCG test was performed to diagnose pregnancy for patients with missed menstrual period. Clinical pregnancy was diagnosed 2 weeks after a positive test by ultrasound, indicating the presence of an intrauterine gestational sac with a fetal cardiac activity (FCA).

**Clinical outcome**

The primary outcome: overall clinical pregnancy rate (positive FCA). Also the incidence of live birth, miscarriage, ectopic, multiple gestation and OHSS were evaluated.
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Table 1: Pre and post preparation semen parameters

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<tr>
<th></th>
<th>Before preparation</th>
<th>After preparation</th>
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<tbody>
<tr>
<td></td>
<td>mean</td>
<td>SD</td>
</tr>
<tr>
<td>Count</td>
<td>61</td>
<td>38</td>
</tr>
<tr>
<td>Morphology</td>
<td>18</td>
<td>10</td>
</tr>
<tr>
<td>Total motility</td>
<td>60</td>
<td>18</td>
</tr>
<tr>
<td>Progressive motility</td>
<td>39</td>
<td>17</td>
</tr>
</tbody>
</table>

Figure 1: Indication for IUI

Results

The study population was infertile couples who were attending the Assistant Reproduction Technology Teaching Centre, Albayda-Libya. During the study period, 2500 couples were attending the centre and 121 couples were candidate for IUI. All female partners’ age of this studied group ranged between 19 and 45 years, 20% of them were with advanced maternal age (AMA>42 years). The female participations were with a wide range of Body Mass Indexes (BMI) (19 to 50kg/m²). Tab 2 shows the female partner characteristics. Wide varieties of diagnostic etiologies were represented within the pool of IUI-treated patients of our study. Figure 1 represents the number of each category for IUI indication.

As shown in Figure 2: out of 121 couples; five cases were not eligible to be included in the study after the initial assessment:
2 cases of borderline ovarian malignancy, 2 cases of uncontrolled diabetes mellitus, one case of multiple uterine myomas. 116 couples were enrolled for COH and IUI cycles. During the follow up, 13 patients were cancelled, with a cancellation rate of 11.2%; 10 patients have poor response to ovulation induction treatment and 3 were at high risk for developing life-threatening OHSS. 103 IUI cycles were completed and included in the final data analysis.

**Figure 2:** Flowchart of patients’ selection

<table>
<thead>
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<th>Mean</th>
<th>SD</th>
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</thead>
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<tr>
<td>Age</td>
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<td>6.1</td>
</tr>
<tr>
<td>BMI</td>
<td>30.2</td>
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<tr>
<td>Basal FSH</td>
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<tr>
<td>Basal LH</td>
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<tr>
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</tr>
<tr>
<td>TSH</td>
<td>2.5</td>
<td>3.6</td>
</tr>
<tr>
<td>AMH</td>
<td>1.3</td>
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</tr>
</tbody>
</table>

**Table 2:** Female partners characteristics
A total of 16 pregnancies were recorded in the COH and IUI patients enrolled in the study. The overall clinical pregnancy rate was 15.5%. 8% gave birth to single live birth. All singletons ended at 38-40 weeks, most of them delivered by elective caesarean section and the mothers and their offspring were well and healthy. Seven patients had aborted with a miscarriage rate of 5.8%, all miscarriages occurred in the first trimester. One patient had ectopic pregnancy (rate of ectopic pregnancy was 0.9%) and the patient had left salpingectomy. There was one case of triplet pregnancy and the mother gave birth at 31 weeks of gestation by emergency caesarean section because of abruption placenta (two healthy boys and one healthy girl). Neither case of twins pregnancy, nor OHSS was recorded. No fetal congenital anomalies were recorded in our newborns.

**Discussion**

Empirically IUI has been widely used as an infertility treatment modality [13]. However, the Superiority of IUI compared to that of expectant management or IVF is debatable. Comparing to expectant management, IUI with ovulation stimulation might improve the clinical outcomes [14-15].

The success rate of IUI with or without ovarian stimulation is lower than that of the assisted reproductive technologies (ART) [16]. Nevertheless, COH+IUI require less frequent clinic visits, relatively less invasive and inexpensive when compared to ART [17]. In the literature, the pregnancy rate following IUI showed a wide variation [18-19]. These conflicting results could be a result of variations in the selected treatment group such as type, etiology, and duration of subfertility, female couple’s age, BMI and basal hormonal levels, subfertility diagnostic criteria, treatment regimens or number of IUI cycles [9, 20-24].

In this study, an attempt was made to evaluate the clinical outcome of COH and IUI in our Teaching ART center. The overall clinical pregnancy rate (PR) was 15.5%, which was higher than the PR of IUI reported by other studies 9% [25-26]. Other authors reported a clinical higher pregnancy rate of 17.09%-19% per cycle following COH and IUI; however, these studies were conducted on PCOS patients [27-28]. Furthermore, a much higher success rate per cycle (35.5%) after IUI for a selected group of PCOS patients with low or normal body mass index was reported [29]. A study conducted in 2015 reported a pregnancy rate of 16.5%, after COH+IUI that was comparable to ours [25]. The rate of miscarriage in the current study was 5.8% that was comparable to a rate of 5.4% reported by a previous study [29] but much lower than a miscarriage rate of 15.4% mentioned by Sorouri, et al [30].

The only recorded multiple pregnancy in this study was one case of triplet pregnancy. Other studies reported a higher incidence of multiple gestation after IUI [25] reported that all the recorded clinical pregnancies in their study were multiple gestation. A higher incidence of twins (20%) and higher-order (39%) multiple pregnancies were reported by others [9, 31].

In the current study a unilateral ectopic pregnancy occurred in one patient (0.9%). Others reported much higher rate of ectopic pregnancy 9.1% [30]. Even simultaneous bilateral ectopic pregnancies and heteroctopic pregnancy after IUI have been documented [32, 33].

Previous studies of IUI cycles reported development of OHSS in patients treated either by conventional or minimal stimulation protocols [34-36]. In the present study, 3 IUI cycles were cancelled during the follow up because they were at risk for OHSS but no case of OHSS was documented. Similarly, Kamath, et al (25) did not report any case of OHSS during their IUI cycles.

The none occurrence of OHSS and the low incidence of multiple gestation in the current study might reflect the choice of appropriate stimulation protocols and the proper patients follow up in an attempt to achieve a balance between a
suitable success rate without increasing the risk of multiple pregnancy or the life-threatening OHSS. In selected cases of subfertility, IUI provide a reasonable chance of conception and should be considered as a first line approach prior to moving to more invasive and expensive IVF treatment [9,24].

The success in IUI is multifactorial, and therefore, there is still debate about the effective factors in patients' selection and optimal protocol to be used in an attempt to improve pregnancy rate after IUI. Future work to be conducted to investigate the factors that could improve the IUI outcome.

**Conclusion**

This study achieved a success rate comparable to the other infertility treatment centers without increase in the incidence of multiple gestation or ovarian hyperstimulation syndrome.

**References**


