Infertility Clinical Guideline
Intrauterine Insemination

Purpose:
- To define treatment parameters for intrauterine insemination.

Goals:
- To provide an evidence-based approach to infertility management.
- To describe the limitations of and recommendations for treatment.

Background

- Intrauterine insemination (IUI) involves the placement of washed, motile sperm directly into the uterine cavity.
- Indications for IUI
  - Sexual dysfunction
  - Cervical trauma
  - Mild male factor infertility
  - Unexplained infertility
- There is no evidence that, absent sexual dysfunction or cervical trauma, natural cycle (i.e. no ovarian stimulation) IUI has any benefit over appropriately timed heterosexual intercourse
  - Natural cycle IUI may be considered in the setting of donor insemination when no other infertility factor is present
- There is no evidence from the published studies that intrauterine insemination is an effective treatment for cervical hostility. (Cochrane Database 2009)
- A single timed insemination per cycle is sufficient as there is no benefit to additional inseminations per cycle (Osuna et al.; Alborzi et al.; Tonguc et al.)
- Assisted Reproductive Technologies (ART) should be the treatment of choice for all women with diminished ovarian reserve
  - Little benefit is obtained from converting a poor response ART cycle to IUI when at least 2 follicles are present (Nicopoullos and Abdalla; Norian, et al)
- Benefit of IUI cycles
  - After 6 cycles of gonadotropin/IUI the cumulative pregnancy rate ranges from 0 to 48.5%. (Merviel et al, Boulghar)
  - The pregnancy rate per cycle appears to diminish after the 3rd cycle (Merviel et al. al, )
  - After 3 cycles of gonadotropin/IUI 39.2 to 87% of conceptions will have
occurred (Merviel et al, Aboulghar, Sahakyan, Dickey)

- After 4 cycles of gonadotropin/IUI 89 to 98% of conceptions will have occurred. (Merviel et al, Aboulghar, Sahakyan, Nuojua-Huttunen Dickey)

- Clomiphene Citrate may be as effective as gonadotropins when used in conjunction with IUI in cases of cervical factor, mild male factor and unexplained infertility
  - Pregnancy rates for clomid/IUI (2%-19.3%) do not differ from those involving gonadotropin/IUI (7%-19.2%) or low dose (75 IU/day) gonadotropin/IUI (8.7%-16.3%) but the incidence of twin gestations is markedly reduced (12.5% vs. 28.6% and 29.3% respectively). (McClimrock et al.)
  - Cumulative pregnancy rates within 4 cycles are 51.44% and 25.4% for clomiphene and gonadotropins respectively (the difference in pregnancy rates is not statistically significant). (Ecohard et al, Guzik et al, Reindollar 2010)
  - After 6 cycles of gonadotropin/IUI the cumulative pregnancy rate ranges from 0 to 48.5%. (Merviel et al, Aboulghar)
  - The pregnancy rate per cycle appears to diminish after the 3rd cycle (Merviel et al, )

- Women 38-39 have a diminished prognosis following 2 gonadotropin/IUI cycles and women ≥ 40 have a diminished prognosis after one cycle, (Sahakyan, Isiah et al)

- Women ≥ 41 have a diminished prognosis with clomiphene citrate/IUI treatment. (Aboughar)

- Initial treatment with ART appears to be the most effective strategy for women ≥38 with unexplained infertility. (Reindollar 2011)

- Menopausal levels of FSH range from 25.8 – 134.8 mIU/ml (NLM)

- FSH levels in and of themselves may not be solely and entirely predictive of pregnancy outcome particularly in women < 35
  - FSH levels should be evaluated in conjunction with additional predictors of cycle success including antimüllerian hormone (AMH), antral follicle count (AFC) as well as follicular response to stimulation and in the case of Assisted Reproductive Technology (ART), oocyte quantity and quality
  - Each infertility program should define and validate its threshold value of FSH that determines diminished ovarian reserve
    - Delivery rates for women with diminished ovarian reserve in excess of defined threshold levels of FSH are reported to be approximately 1% (Scott)
    - Older women (age >40 years) with an elevated FSH (on day 3 of the menstrual cycle) may not be candidates for undergoing ART, as they may have significantly lower implantation rates and clinical pregnancy rates, compared with a normal day 3 FSH in
the same age category. (Luna et al)

- ART should be the treatment of choice for all women with diminished ovarian reserve
- Failure to respond to stimulation or inadequate oocyte production or quality, fertilization and/or embryo development should lead to alternate treatment (e.g. ovum donation) or cessation of treatment (ASRM)

**Client Target Population**

This guideline applies to all couples/individuals considering treatment with intrauterine insemination.

**Treatment**

- If IUI is to be performed at all, it should be limited to 3-4 cycles and no more than 6 (in the presence of ovulatory dysfunction) for women <35
- Women ≥35 who are contemplating IUI should be directed to ART
- Clomiphene citrate should be the agent of choice for most patients to stimulate folliculogenesis during superovulation when used in conjunction with IUI (Ecochard et al, Guzick et al, Reindollar 2010)
  - Letrozole or gonadotropins may be considered for use when clomiphene citrate results in a thin endometrial lining (<7mm) or is associated with side effects such as headaches or visual symptoms
  - Although an increased number of follicles may be obtained with gonadotropins, pregnancy rates are equivalent to stimulation with clomiphene citrate, while the risk for a multiple gestation is significantly increased with gonadotropins.

**Best Practices**

- ART should be the initial treatment of choice for the treatment of most infertility factors (Reindollar 2011)
  - Ovulation induction may be utilized for ovulatory factors. In anovulatory infertile women, failure to achieve pregnancy after 3 to 6 cycles of successful ovulation induction should prompt a move to ART (ASRM-2)
  - A limited trial of clomiphene citrate/IUI may be considered for women <35
- Natural cycle IUI may be considered in the setting of sexual dysfunction, cervical trauma or donor insemination when no other infertility factor is present

**Medical Director Escalation**

- All cases of clomiphene citrate/IUI beyond the 4th cycle should be reviewed by the Medical Director
  - Obtain stimulation sheets from all cycles for medical director review
- All cycles of gonadotropin/IUI for unexplained infertility or male factor infertility should be reviewed by the Medical Director
  - Obtain medical records relevant to the infertility diagnosis and rationale for treatment from the provider for medical director review.
- Medical director review is indicated for all cases of elevated FSH prior to cycle start to assess additional predictors of success (e.g. AFC, AMH, prior cycle history)
### Case Examples

#### Case 1:
A 34 year old woman and her 37 year old male partner present with a history of infertility of 12 months duration. A semen analysis is normal and a HSG demonstrates bilateral fallopian tubal patency. She has regular menstrual cycles. A day 3 FSH level comes back as 10 mIU/ml. While this level suggests the potential for diminished ovarian reserve, egg quality should still be good given her age. While ART is a very reasonable treatment option, she and her partner prefer to pursue a more “conservative” approach initially. The couple is advised that with clomiphene citrate/IUI she might expect that a pregnancy, if it were to occur, should happen within 4 treatment cycles. Despite what appears to be adequate unfollicular development and good quality sperm at the time of intrauterine insemination, she does not conceive. Although they have heard that injectable drugs are typically the “next step” in treatment, once they learn that pregnancy rates are not improved compared to clomiphene and that the risk of a multiple gestation is increased, the couple agrees to proceed to ART. After 4 cycles, an IVF cycle is initiated. On the day of retrieval, 6 mature oocytes are obtained, 5 of which fertilize. On day 5 of embryo culture, a single expanded blastocyst embryo is electively transferred and two blastocysts are cryopreserved. A successful singleton gestation is achieved.

#### Case 2:
A 39 year old patient and her 36 year old husband present for further infertility treatment. She has been diagnosed with unexplained infertility elsewhere and has undergone 2 gonadotropin/IUI cycles. Although she has produced 4 follicles with each stimulation cycle, she has not conceived. She would like to pursue additional gonadotropin/IUI cycles. Her FSH is 9.0 mIU/ml. This patient and her husband are advised that the chance for conception plateaus after 4 stimulated IUI cycles and that ART is a more efficacious route to pursue. After explaining the risks and benefits of ART, the couple agrees to pursue ART. On her first cycle, she is stimulated with Gonal F 225 IU/day for 12 days. Although only 3 mature follicles develop, they elect to go to retrieval. Only two poor quality oocytes are retrieved. On the next ART attempt, the dosage of Gonal F is increased to 375 IU/day. Six oocytes are retrieved, two of which fertilize. The embryos arrest on day 3 in culture at a 4 cell stage. At this time, ovum donation is discussed but the couple prefers to attempt another ART cycle. Given the results of the 2 ART cycles, additional ART cycles are deemed to have <1% prognosis. Ovum donation, adoption or cessation of treatment are the next appropriate steps.

#### Case 3:
A 26 year old female and her 25 year old male partner present for an infertility evaluation and treatment. A semen analysis demonstrates azoospermia. Further urological evaluation reveals complete spermatid maturation arrest. The couple elects to pursue donor insemination. As no other infertility factor has been identified, the couple attempts 2 natural cycle inseminations with donor sperm. Unsuccessful, the third cycle utilizes a course of clomiphene citrate. A singleton gestation is achieved.


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Bibliography
## History

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