

Assessment and treatment for infertile couples

Clinical specialty: Obstetrics and Gynecology

Intended users: Physicians and students

Source of Evidence: The Cochrane Library and DARE

JC Objective

To discuss the evidence for the Assessment and treatment for infertile couples

Background

1. Infertility is defined as 1 year of regular unprotected sexual intercourse without conception, suggesting a diminished capacity to conceive and reproduce. In contrast to sterility, infertility is not an irreversible state.
 - a. **Primary infertility** is applied to the couple who has never achieved a pregnancy;
 - b. **Secondary infertility** implies that at least one previous conception has taken place
2. People who are concerned about their fertility should be informed that about 84% of couples in the general population will conceive within 1 year if they do not use contraception and have regular sexual intercourse. Of those who do not conceive in the first year, about half will do so in the second year (cumulative pregnancy rate 92%).

Recommendations

When to start evaluation?

1. **RULE**: couples who have not conceived after 1 year of unprotected intercourse are candidates for infertility evaluation.
2. **Earlier investigation** is recommended based on
 - a. Woman's Age.
 - i. 35-40 years of age: evaluation after 6 months
 - ii. >40 years of age: immediate evaluation
 - b. start immediately if there is any risk factors such as Irregular or absent periods, History of PID, endometriosis, IUD use, previous ectopic pregnancy.

Investigation

Semen analysis

1. Initial analysis
 - Volume: 2.0 ml or more
 - Liquefaction time: within 30 minutes
 - pH: 7.2 or more
 - Sperm concentration: 20 million spermatozoa per mL or more
 - Total sperm number: 40 million spermatozoa per ejaculate or more
 - Motility: 50% or more motile (grades a and b) or 25% or more with progressive motility (grade a) within 60 minutes of ejaculation
 - i. Grade a: rapid progressive motility.
 - ii. Grade b: slow or sluggish progressive motility.
 - Viability: 75% or more live
 - Morphology: 70% or more normal
 - White blood cells: fewer than 1 million per mL
2. If the result of the first semen analysis is abnormal, a repeat confirmatory test should be offered.
 - Repeat confirmatory tests should ideally be undertaken 74 days after the initial analysis to allow time for the cycle of spermatozoa formation to be completed.
 - If a gross spermatozoa deficiency (azoospermia or severe oligozoospermia) has been detected, the repeat test should be undertaken as soon as possible.
3. Screening for antisperm antibodies ??
4. serum FSH (marker for seminiferous tubule failure)
5. testicular biopsy

Assessing ovulation

1. History of the frequency and regularity of menstrual cycles. Women with regular monthly menstrual cycles are **likely** to be ovulating.
2. Diagnostic tests that **detect** ovulation
 - a. *Midluteal serum progesterone levels*: normal luteal phase: 6-30 ng/ml
 - b. basal body temperature (BBT) chart ??
 - c. Endometrial biopsy
3. Diagnostic tests that **predict** the time of ovulation
 - a. TVUS folliculometry
 - i. It can also give presumptive evidence of ovulation (the disappearance of a dominant follicle combined with the presence of free fluid in the cul-de-sac)
4. Tests of ovarian reserve currently have limited sensitivity and specificity in predicting fertility.
 - a. high levels of basal FSH indicate reduced ovarian reserve.
5. Further tests
 - a. FSH and LH: if there is oligomenorrhea or amenorrhea
 - b. Prolactin: if there galactorrhea
 - c. Thyroid function: if there are symptoms of thyroid disease.
 - d. Dated endometrial biopsy to evaluate the luteal phase

Assessing tubal damage

1. Women who are not known to have comorbidities (such as PID, previous ectopic pregnancy, or endometriosis)
 - a. Hysterosalpingography (HSG) to screen for tubal occlusion: reliable test for ruling out tubal occlusion and is less invasive and makes more efficient use of resources than laparoscopy.
 - b. Hysterosalpingo-contrast-ultrasonography is an effective alternative to HSG.
2. Women who are known to have comorbidities: laparoscopy and dye to assess tubal and other pelvic pathology.

Assessing uterine abnormalities

Hysteroscopy if clinically indicated

Postcoital testing of cervical mucus

The routine use of postcoital testing of cervical mucus in the investigation of fertility problems is not recommended because it has no predictive value on pregnancy rate.

Interventions

Health Education: sexual intercourse every 2 to 3 days optimizes the chance of pregnancy. Timing intercourse to coincide with ovulation causes stress and is **not recommended**.

Male Factor

1. Medical management
 - a. Hypogonadotropic hypogonadism: gonadotrophin drugs
 - b. Idiopathic semen abnormalities should not be offered antiestrogens, gonadotropins, androgens, or bromocriptine because they have not been shown to be effective.
 - c. Significance of antisperm antibodies is unclear and the effectiveness of systemic corticosteroids is uncertain.
2. Surgical management
 - a. obstructive azoospermia
 - i. surgical sperm recovery and IVF.
 - ii. Surgical correction. Surgical correction should be considered as an alternative to
 - b. Surgery for varicoceles as a form of fertility treatment does not improve pregnancy rates.
3. ART according to severity of male factor

Severity of Male factor	Sperm Concentration	Motility
Mild	15-20 million spermatozoa per mL	40-50%
Moderate	10-15 million spermatozoa per mL	20-40%
Severe	<10 million spermatozoa per mL	<20%

Female Factors

Ovulation Induction: JC for PCOS

Management of Endometriosis: JC for Endometriosis

Tubal and Uterine Surgery

1. For women with mild tubal disease tubal surgery may be more effective than no treatment. It may be considered as a treatment option.
2. There was no evidence for or against the use of
 - a. CO2 laser versus standard techniques for adhesiolysis (OR for pregnancy 1.07, 95% CI 0.40 to 2.87) or salpingostomy (OR for pregnancy 1.38, 95% CI 0.47 to 4.05).
 - b. laparoscopy versus laparotomy.
 - c. prosthesis at salpingostomy versus non-use
 - d. Cuff versus Bruhat technique for salpingostomy.
 - e. thermocoagulation versus electrocoagulation at adhesiolysis.
3. For women with proximal tubal obstruction, selective salpingography plus tubal catheterisation, or hysteroscopic tubal cannulation, may be treatment options.
4. Women with intrauterine adhesions should be offered hysteroscopic adhesiolysis because this is likely to restore menstruation and improve the chance of pregnancy.

Intrauterine Insemination

1. Couples with mild male factor, unexplained infertility, or minimal to mild endometriosis should be offered up to **six cycles of IUI** because this increases the chance of pregnancy.
2. to manage male factor fertility problems
 - a. IUI + OH versus IUI: OR 1.47, 95% CI 0.92 to 2.37
3. to manage unexplained infertility
 - a. IUI versus TI, both in stimulated cycles: OR 1.68, 95% CI 1.13 to 2.50.
 - b. IUI with OH versus IUI in a natural cycle: OR 2.33, 95% CI 1.46 to 3.71
4. to manage minimal or mild endometriosis
 - a. IUI + OH increases pregnancy rates compared with no treatment
5. Single rather than double insemination should be offered.
6. OH protocols for IUI
 - a. gonadotrophins versus clomiphene: OR 1.8, 95% CI 1.2 to 2.7.
 - b. comparing different types of gonadotrophins: no difference.
 - c. no evidence of benefit in doubling the dose of gonadotrophins (OR 1.2 95% 0.67 to 1.9) although the multiple pregnancy rates and OHSS rates were increased.
 - d. clomiphene versus aromatase inhibitors: OR 1.2 95% CI 0.64 to 2.1.
 - e. adding a GnRH agonist which did not improve pregnancy rates (OR 0.98 95% CI 0.6 to 1.6),
7. Sperm preparation for IUI
 - a. No evidence of a difference between pregnancy rates 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)

In Vitro Fertilization

Clinical effectiveness and referral for IVF

1. Couples in which the woman is aged 23–39 years at the time of treatment and who have an identified cause for their infertility (such as male factor, bilateral tubal occlusion, endometriosis) or who have infertility of at least 3 years' duration should be offered up to three stimulated cycles of IVF.

Factors Affecting the Outcome of IVF

1. Surgery for hydrosalpinges before IVF
 - a. Women **with hydrosalpinges** should be offered salpingectomy or tubal occlusion before IVF
 - i. clinical pregnancy (OR 2.31, 95%CI 1.48 to 3.62) increased with laparoscopic salpingectomy for hydrosalpinges prior to IVF.
 - ii. Laparoscopic occlusion of the fallopian tube versus no intervention: clinical pregnancy (OR 4.66, 95%CI 2.47 to 10.01)
 - iii. Comparison of tubal occlusion to salpingectomy did not show a significant advantage of either surgical procedure in terms of ongoing pregnancy (OR: 1.65, 95%CI 0.74, 3.71) or clinical pregnancy (OR 1.28, 95%CI 0,76 to 2.14).
 - iv. efficacy of ultrasound guided aspiration ??
2. Female age
 - a. optimal female age range for IVF is 23–39 years. Chances of a live birth per treatment cycle:
 - i. >20% for women aged 23–35 years
 - ii. 15% for women aged 36–38 years
 - iii. 10% for women aged 39 years
 - iv. 6% for women aged 40 years or older.
 - b. effectiveness of IVF in women younger than 23 years is uncertain because very few women in this age range have IVF.
3. Number of embryos to be transferred and multiple pregnancy
 - a. the chance of multiple pregnancy following IVF depends on the number of embryos transferred per cycle of treatment. To balance the chance of a live birth and the risk of multiple pregnancy and its consequences, no more than two embryos should be transferred during any one cycle of IVF.
4. Number of previous treatment cycles
 - a. the chance of a live birth following IVF is consistent for the first three cycles of treatment, but that the effectiveness after three cycles is less certain.
5. Pregnancy history
 - a. IVF is more effective in women who have previously been pregnant and/or had a live birth.
6. Alcohol, smoking and caffeine consumption
 - a. reduce the effectiveness of ART procedures, including IVF
7. Body weight
 - a. female BMI should ideally be in the range 19–30 before commencing ART, and that a female BMI outside this range is likely to reduce the success of ART procedures.

GIFT and ZIFT

There is insufficient evidence to recommend the use of gamete intrafallopian transfer or zygote intrafallopian transfer in preference to IVF in couples with unexplained infertility or male factor.

Procedures Used during IVF

1. Ovulation induction during in vitro fertilisation treatment
 - a. Gonadotrophin use during IVF: HMG, uFSH, and rFSH are equally effective in achieving a live birth when used following pituitary down-regulation as part of IVF.
 - b. Natural cycle IVF has lower pregnancy rates per cycle of treatment than clomiphene citrate-stimulated and gonadotrophin-stimulated IVF and is therefore not recommended.
 - c. For women who have regular ovulatory cycles, the likelihood of a live birth after replacement of frozen-thawed embryos is similar whether the embryos are replaced during natural or stimulated cycles.
 - d. The use of adjuvant growth hormone with gonadotrophins during IVF cycles does not improve pregnancy rates and is not recommended.
2. GnRH analogues during IVF
 - a. The routine use of gonadotrophin-releasing hormone agonist in long protocols during IVF is recommended.
 - i. For pituitary down-regulation as part of IVF, using GnRH agonist in addition to gonadotrophin stimulation facilitates cycle control and results in higher pregnancy rates than the use of gonadotrophins alone.
 - b. The use of gonadotrophin-releasing hormone antagonists is equally effective
3. Oocyte maturation – human chorionic gonadotrophin
 - a. In effecting oocyte maturation, recombinant human chorionic gonadotrophin achieves similar results to urinary human chorionic gonadotrophin in terms of pregnancy rates and incidence of ovarian hyperstimulation syndrome.
4. Monitoring of stimulated cycles
 - a. Ultrasound monitoring of ovarian response should form an integral part of the IVF cycle.
 - b. Monitoring E2 levels during ovulation induction as part of IVF
5. Oocyte retrieval
 - a. Women undergoing transvaginal retrieval of oocytes should be offered sedation because it is a safe and acceptable method of providing analgesia.
 - b. Follicle flushing does not increase the numbers of oocytes retrieved or pregnancy rates, and it increases the duration of oocyte retrieval and associated pain.
6. Assisted hatching
 - a. Assisted hatching is not recommended because it has not been shown to improve pregnancy rates.
7. Embryo transfer techniques
 - a. Women undergoing IVF should be offered ultrasound-guided embryo transfer because this improves pregnancy rates.
 - b. Embryo transfers on day 2 or 3 and day 5 or 6 appear to be equally effective in terms of increased pregnancy and live birth rates per cycle started.
 - c. Replacement of embryos into a uterine cavity with an endometrium of less than 5 mm thickness is unlikely to result in a pregnancy and is not recommended.

- d. Women should be informed that bed rest of more than 20 minutes' duration following embryo transfer does not improve the outcome of IVF.
 - e. Embryos not transferred during a stimulated IVF cycle may be suitable for freezing. If two or more embryos are frozen then they should be transferred before the next stimulated treatment cycle.
8. Luteal support
- a. women who are undergoing IVF using GnRH agonists for pituitary down-regulation should be informed that luteal support using hCG or progesterone improves pregnancy rates.
 - b. The routine use of hCG for luteal support is not recommended because of the increased risk of OHSS.
9. ICSI
- a. Indications for intracytoplasmic sperm injection
 - i. Severe deficits in semen quality
 - ii. Obstructive azoospermia
 - iii. Epididymal or testicular sperm
 - iv. Frozen thawed sperm with poor survival
 - v. Absent fertilization in prior IVF cycle
 - b. Intracytoplasmic sperm injection versus in vitro fertilisation
 - i. ICSI improves fertilisation rates compared to IVF alone, but once fertilisation is achieved the pregnancy rate is no better than with IVF.
10. Sperm recovery
- a. Surgical sperm recovery before ICSI may be performed using several different techniques. In all cases, facilities for cryopreservation of spermatozoa should be available.
 - b. Epididymal spermatozoa retrieval
 - i. Micro surgical epididymal sperm aspiration (MESA)
 - ii. Percutaneous epididymal sperm aspiration (PESA)
 - c. Testicular spermatozoa retrieval
 - i. Open or excisional biopsy TESE
 - ii. Fine-needle TESA