PERCORSO GONADI 2

Roma,
9-11 novembre 2012

INQUADRAMENTO DELL'INFERTILITA' DI COPPIA

OPZIONI TERAPEUTICHE

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DIPARTIMENTO DI MEDICINA CLINICA E MOLECOLARE
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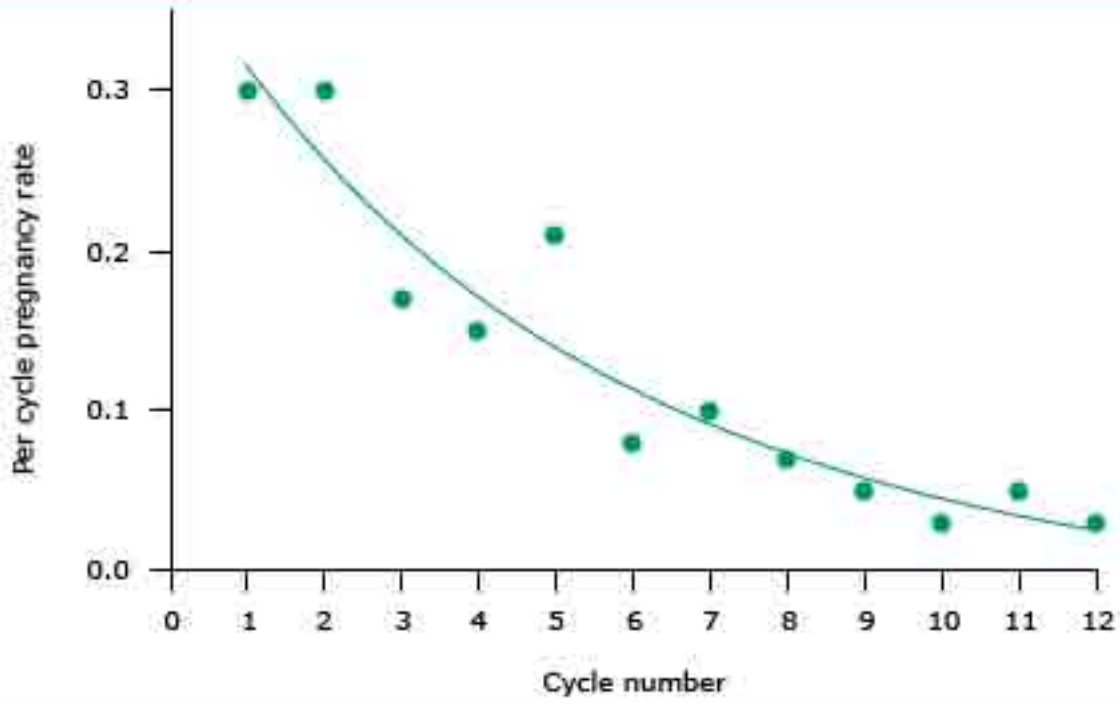
AZIENDA OPEDALIERA SANT'ANDREA

Fecundability in a cohort of healthy couples attempting to conceive



Data from: Zinaman, MJ, Clegg, ED, Brown, CC, et al. Estimates of human fertility and pregnancy loss. Fertil Steril 1996; 65:503.

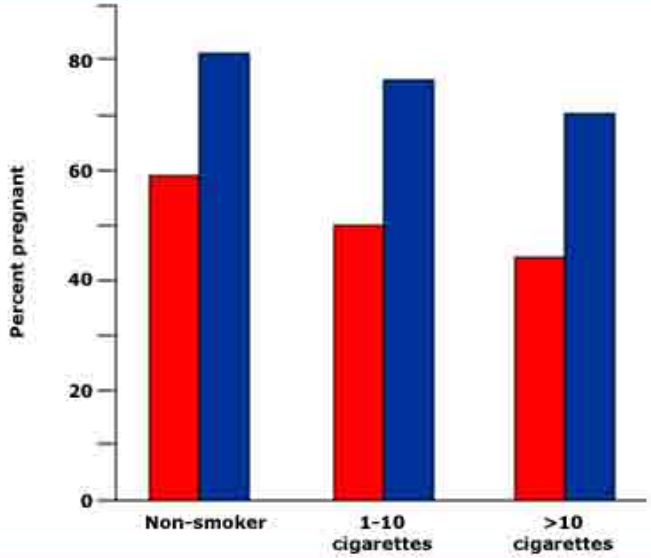
UpToDate

General principles of management of infertile couples

Involve both partners in the evaluation and management of infertility
Recommend lifestyle modifications to enhance fertility
Couple - smoking cessation and reduce exposure to potential environmental toxins
Women - abstinence from alcohol, reduction of excessive caffeine intake, weight modulation to achieve target body mass index (20-25 kg/m2)
Perform infertility evaluation according to established guidelines
Identify causes of infertility
Reversible causes - implement medical or surgical therapy to correct the etiology of infertility
Irreversible causes - utilize assisted reproductive technologies, gamete donation, gestational carrier, adoption to overcome the etiology of infertility

UpToDate

Percent of couples achieving pregnancy within 3.5 months (red bars) and 9.5 months (blue bars)



The x axis is the reported smoking status of the female partner. The y axis is the percent of couples achieving pregnancy by the time specified (3.5 months - red bars; 9.5 months - blue bars). Among women who reported smoking >10 cigarettes daily, the percent of couples achieving pregnancy by 3.5 and 9.5 months was significantly decreased compared to couples where the female partner did not smoke. The subjects were women who were pregnant or recently delivered (sample size approximately 4035 women).

Data adapted from: Table 4 in Bolumar, F, Olsen, J, Boldsen, J and the European Study Group on Infertility and Subfecundity. Smoking reduces fecundity: a European multicenter study on infertility and subfecundity. Am J Epidemiol 1996; 143:578-87.

UpToDate

Percent pregnancy loss by maternal age at conception

Maternal age	Spontaneous abortions (percentage)	Ectopic pregnancies (percentage)	Stillbirths rate/1000
12-19	13.3	2.0	5.0
20-24	11.1	1.5	4.2
25-29	11.9	1.6	4.0
30-34	15.0	2.8	4.4
35-39	24.6	4.0	5.0
40-44	51.0	5.8	6.7
>=45	93.4	7.0	8.2

Adapted from: Anderson et al. Figures 2,4,5. The total spontaneous abortion rate is estimated using the assumption that only 80 percent of women with abortions in recognized pregnancies were hospitalized. Adapted from: Anderson FWJ, Johnson TRB. Maternal mortality at Y2K. Postgraduate Obstetrics and Gynecology 2000; 20:1.

Frequency of diseases associated with infertility

	Percent
Female partner	
Ovulatory disorders	25 to 27
Endometriosis	5 to 15
Pelvic adhesions	12
Tubal occlusion	11
Other tubal abnormalities	11
Hyperprolactinemia	7
Male partner	
Abnormal semen analysis	25
Unexplained	17
Other	4

Adapted from data in WHO Scientific Group Report. Recent Advances in Medically Assisted Conception. WHO Technical Report Series 820. Geneva. World Health Organization 1992 and Collins, JA. Unexplained Infertility. In Keye WR, Chang RJ, Rebar RW, Soules MR (eds). Infertility: evaluation and treatment. WB Saunders, Philadelphia 1999, p 249.

PERCORSO GONADI 2

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INQUADRAMENTO
DELL'INFERTILITA' DI COPPIA

Partner maschile

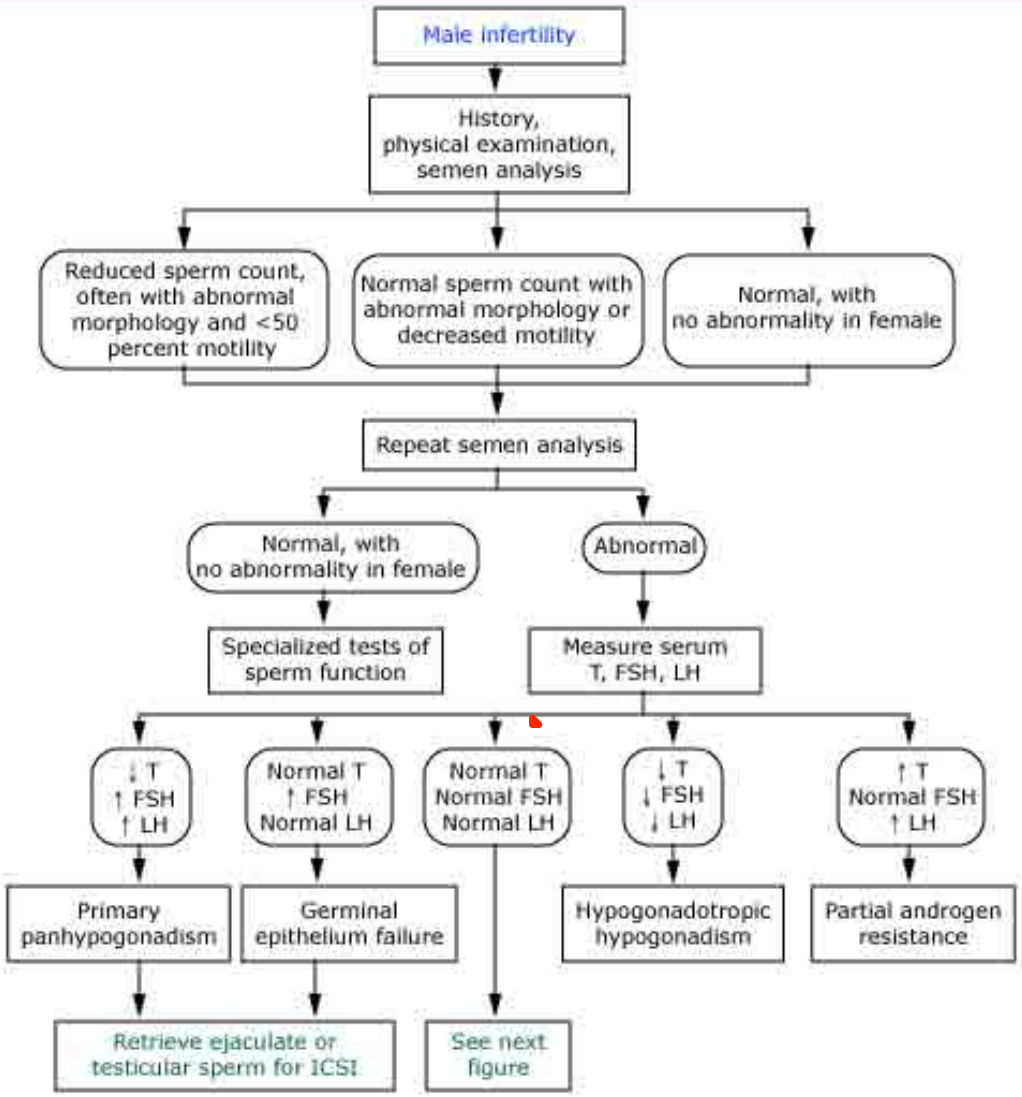
CAUSE PIU' COMUNI DI INFERTILITA' MASCHILE

MALATTIE IPOTALAMO IPOFISARIE	1-2 %
MALATTIE TESTICOLARI	30–40%
MALATTIE POST-TESTICOLARI	10-20 %
NON CLASSIFICABILI	40-50 %

CAUSE PIU' COMUNI DI INFERTILITA' MASCHILE TRATTABILI O NON TRATTABILI SE NON CON TRATTAMENTO ASSISTITO

OSTRUZIONE INTRATESTICOLARE	INTRATTABILE
OSTRUZIONE EPIDIDIMALE	PER LO PIU' INTRATTABILE
OSTRUZIONE VASALE	TRATTABILE
OSTRUZIONE DEI DOTTI EIACULATORI	PER LO PIU' TRATTABILE
TESTICULOPATIA PRIMARIA	INTRATTABILE
EIACULAZIONE RETROGADA	PER LO PIU' TRATTABILE
MANCANZA DI EIACULAZIONE	PER LO PIU' INTRATTABILE
VARICOCELE	TRATTABILE, MA CON EFFETTO VARIABILE
MALATTIE ENDOCRINE	PER LO PIU' TRATTABILE
MALATTIE GENETICHE	PER LO PIU' INTRATTABILE
INFERTILITA' DI ORIGINE AUTOIMMUNE	PER LO PIU' INTRATTABILE

Approach to diagnosis of male infertility



T: testosterone; FSH: follicle-stimulating hormone; LH: luteinizing hormone; ICSI: intracytoplasmic sperm injection.

UpToDate

Nota 74

- Determinazione 27 aprile 2010 (GU 17 maggio 2010, n. 113): modifica alla nota AIFA 74 di cui alla determinazione 23 febbraio 2007, e successivo

- Comunicato di rettifica relativo all'estratto della determinazione del 27 aprile 2010 recante la modifica della nota AIFA 74 (GU 16 giugno 2010, n 138

La prescrizione a carico del SSN, su diagnosi e piano terapeutico di strutture specialistiche, secondo modalità adottate dalle Regioni e dalle Province Autonome di Trento e Bolzano, è limitata alle seguenti condizioni:

· trattamento dell'infertilità maschile:

in maschi con ipogonadismo-ipogonadotropo con livelli di gonadotropine bassi o normali e comunque con FSH non superiore a 8 mUI/ml

IPOGONADISMO IPOGONADOTROPO
TRATTAMENTO CON GONADOTROPINE

Roma,
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QUALI SOGGETTI HANNO PIU' PROBABILITA' DI RISPONDERE?

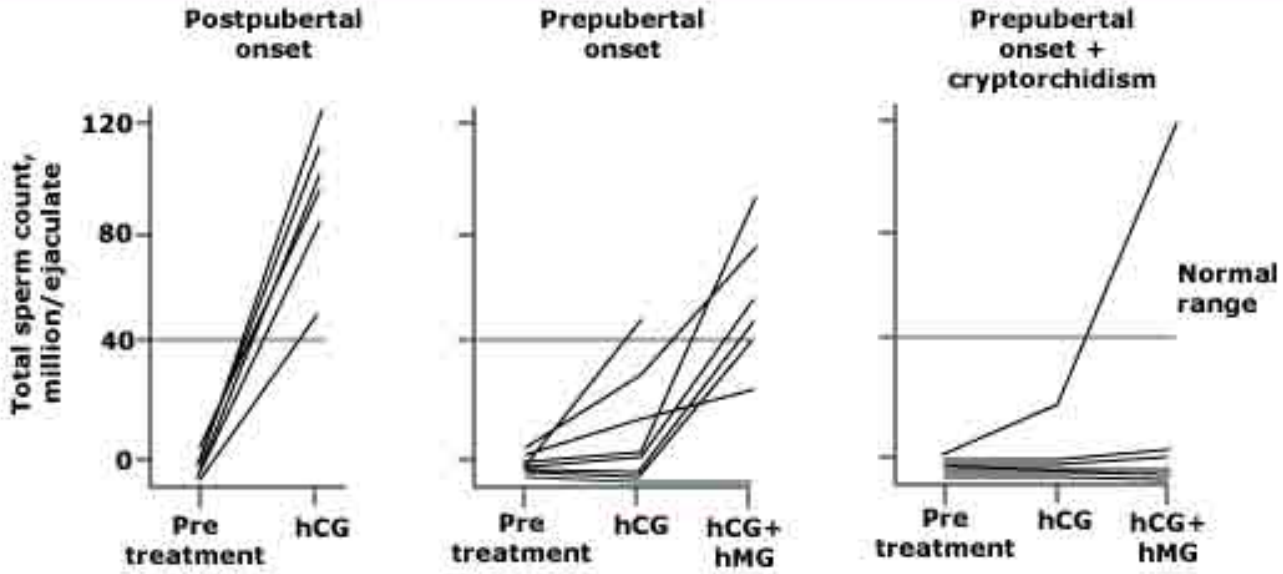
- ✓SVILUPPO DELL'IPOGONADISMO DOPO LA PUBERTA'
- ✓ IPOGONADISMO PARZIALE
- ✓ NO CRIPTORCHIDISMO NEONATALE E COMUNQUE TESTICOLI IN SEDE AD UN ANNO DI VITA
- ✓ PRECEDENTE TRATTAMENTO CON GONADOTROPINE MIGLIORE RISPETTO AL TRATTAMENTO CON TESTOSTERONE

IN QUESTI SOGGETTI IL TRATTAMENTO CON GONADOTROPINE PORTA IN CIRCA IL 90% LA COMPARSA DI SPERMATOZOI SUFFICIENTE PER FECONDARE MA DIFFICILMENTE NELLA NORMA, MENTRE RISPONDE 1/8 DI PAZIENTI CON IPOGONADISMO PREPUBERALE

IPOGONADISMO IPOGONADOTROPO
TRATTAMENTO CON GONADOTROPINE

- ✓ Usare hCG 2000 UI tre volte a settimana i.m. o s.c.
- ✓ Misurare T dopo 3-4 mesi se non compreso tra 400-800 ng/dl incrementare le dosi di hCG di 500 UI
- ✓ Valutare lo spermiogramma , una volta raggiunto il target di T ogni 1-3 mesi, di solito occorrono da 6 a 24 mesi per avere uno numero di spermatozoi sufficiente, se no aggiungere FSH (hMG), che va utilizzato sempre se l'ipogonadismo è insorto prima della pubertà. La dose iniziale è di 75 UI tre volte a settimana nella stessa siringa dell'hCG. Il dosaggio può essere portatato a 150 UI se il numero di spermatozoi non raggiunge i 20 milioni p.e. entro sei mesi.
- ✓Se entro 12 mesi non si hanno risultati accettabili ART
- ✓Se si attiva gravidanza spontanea continuare con solo hCG, nell'ipotesi di una seconda gravidanza

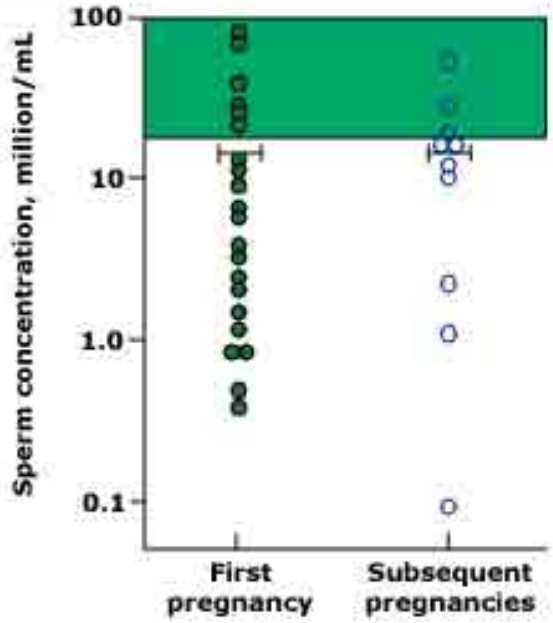
Spermatogenic responses to gonadotropins depending on time of onset of secondary hypogonadism



Sperm counts in men with secondary hypogonadism (idiopathic hypogonadotropic hypogonadism) after treatment with human chorionic gonadotropin (hCG) for six months alone and then, in those in whom the sperm count did not reach the normal range (more than 40 million/ejaculate), for eight months with human menopausal gonadotropin (hMG). Patients with postpubertal onset responded to hCG, those with prepubertal onset generally required the addition of hMG, and those with prepubertal onset and cryptorchidism were primarily resistant to therapy (right panel).

Data from: Finkel DM, Phillips JL, Snyder PJ. Stimulation of spermatogenesis by gonadotropins in men with hypogonadotropic hypogonadism. N Engl J Med 1985; 313:651.

Sperm count at conception in men with secondary hypogonadism



Mean sperm concentration at the time of first pregnancy (left) and subsequent pregnancies (right) in men with isolated hypogonadotropin hypogonadism (IHH, secondary hypogonadism). The horizontal bars represent the mean for each group and the shaded area represents the conventional range of normal. Pregnancy was often achieved at sperm counts well below normal.

Data from: Burris AS, Clark RV, Vantman DJ, Sherins RJ. A low sperm concentration does not preclude fertility in men with isolated hypogonadotropic hypogonadism after gonadotropin therapy. Fertil Steril 1988; 50:343.

PREPARATI DI GONADOTROPINE HP IN COMMERCIO

Gonadotropina corionica umana	PROFASI HP 250,500, 1000, 2000,5000 UI
	GONASI HP 125,250, 500, 1000, 2000,5000 UI
Urofollitropina	METRODIN 75 UI FSH
	FOSTIMON 75, 150 UI FSH
Menotropina	MENOGON 75 UI FSH 75 UI LH
	MEROPUR 75 UI FSH 75 UI LH

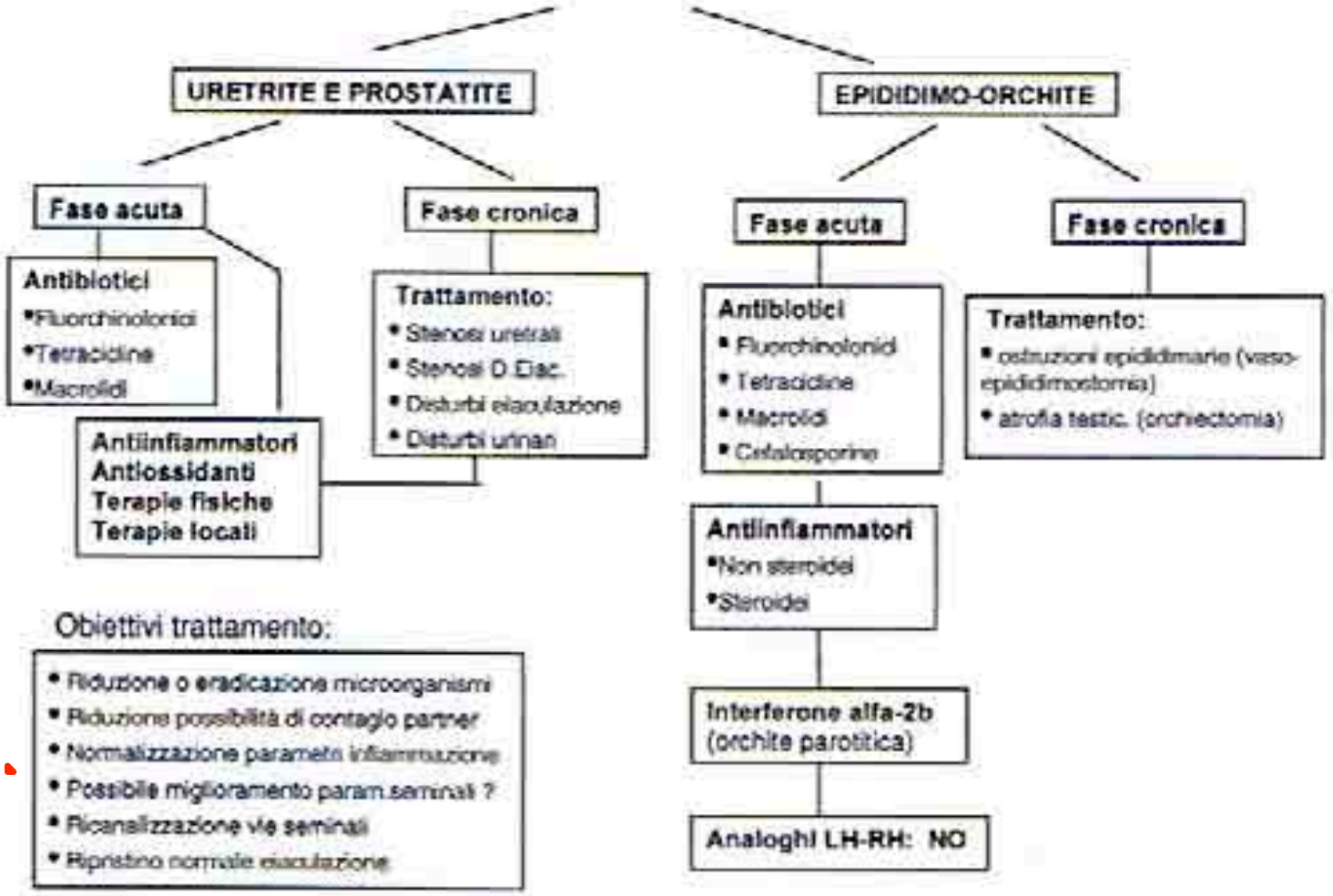
PREPARATI DI GONADOTROPINE rh IN COMMERCIO

Lutropina alfa	LUVERIS 75 UI rhLH
Follitropina beta	PUREGON 900 UI rhFSH
Follitropina alfa / Lutropina alfa	PERGOVERIS 150 UI rhFSH / 75 UI rhLH
Follitropina alfa	GONAL-F 900 UI rhFSH
Coriogonadotropina alfa	OVITRELLE 250 mg (6500 UI) rh hCG

Causes of male factor infertility for which treatment is potentially useful

Etiology	General aspects of treatment
Infections	Antibiotics
Sperm autoimmunity	High-dose glucocorticoids; assisted reproductive techniques - intracytoplasmic sperm injection (ICSI)
Sexual dysfunction	Appropriate therapy
Retrograde ejaculation	Intrauterine insemination (IUI) with washed spermatozoa or assisted reproductive techniques
Varicocele	High ligation or embolization of spermatic veins
Obstructive azoospermia	Microsurgical end-to-end anastomoses (epididymal ducts to epididymal ducts or to vas); microsurgical epididymal sperm aspiration and in vitro fertilization/ICSI

INFEZIONI GENITO-URINARIE E FERTILITA'



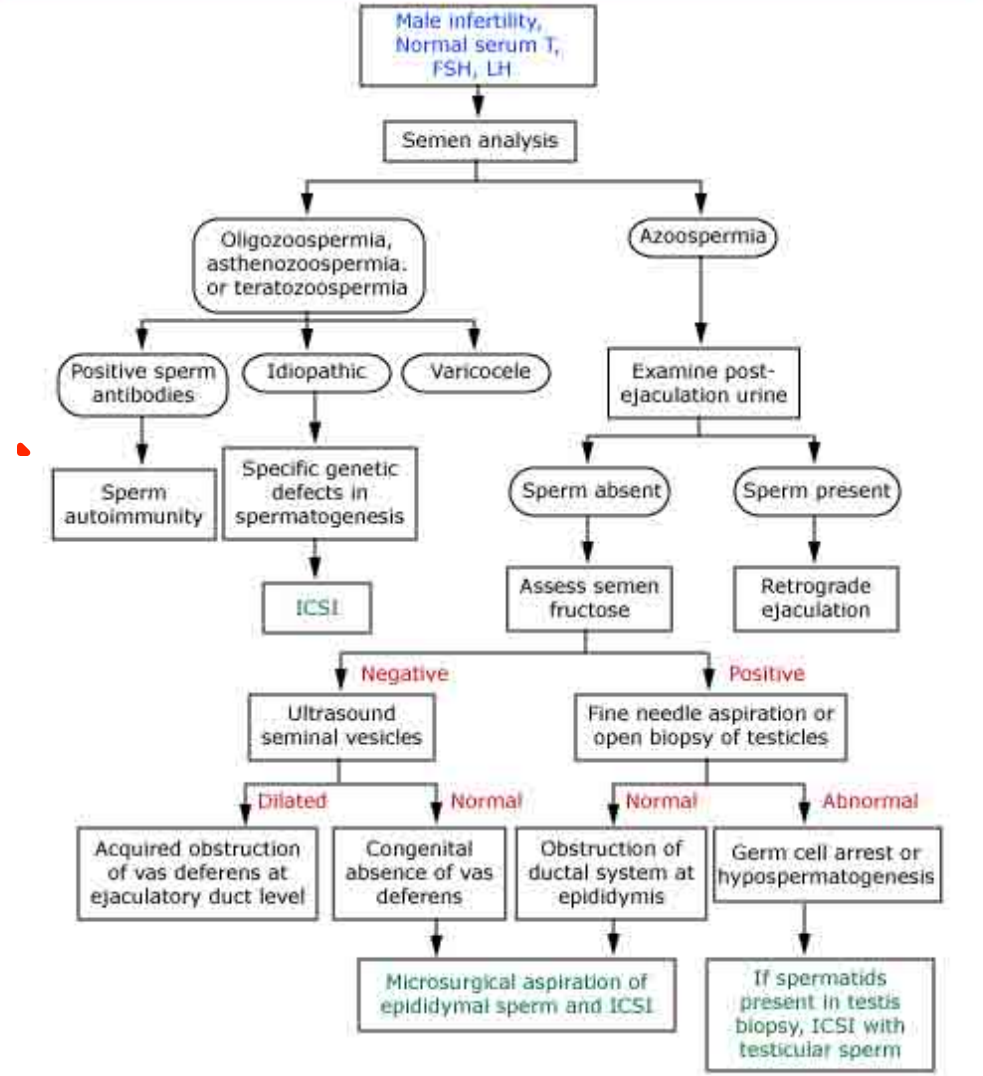
TRATTAMENTO ANTIBIOTICO

✓OTTENERE UNA SPERMIOCULTURA SE I LEUCOCITI SUPERANO IL MILIONE

✓ TRATTARE PAZIENTI CON LEUCOSPERMIA PER 10 GG CON ERITROMICINA O TRIMETOPRIM-SUFAMETOSSAZOLO O CHINOLONICI

✓ SE PERSISTE LEUCOSPERMIA TENTARE UN SECONDO CICLO

Approach to diagnosis of male infertility in patients with normal serum hormone concentrations



T: testosterone; FSH: follicle-stimulating hormone; LH: luteinizing hormone; ICSI: intracytoplasmic sperm injection.

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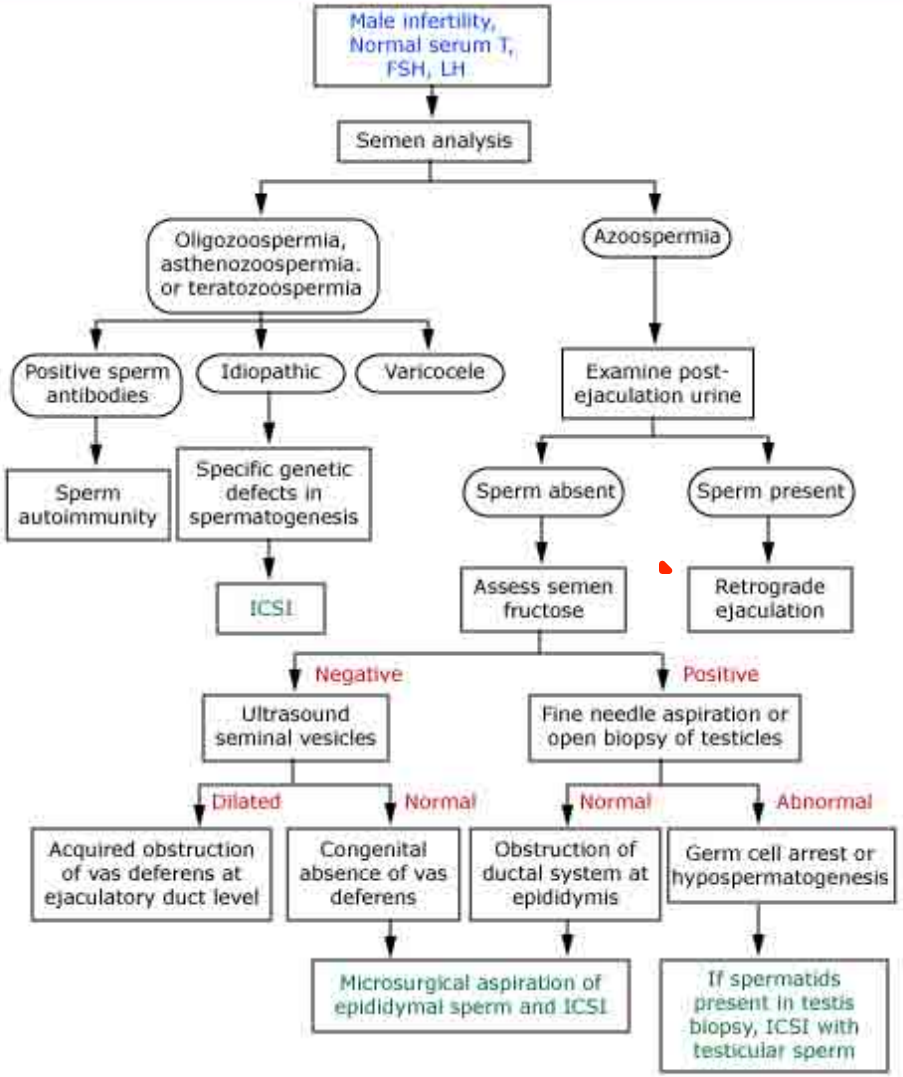

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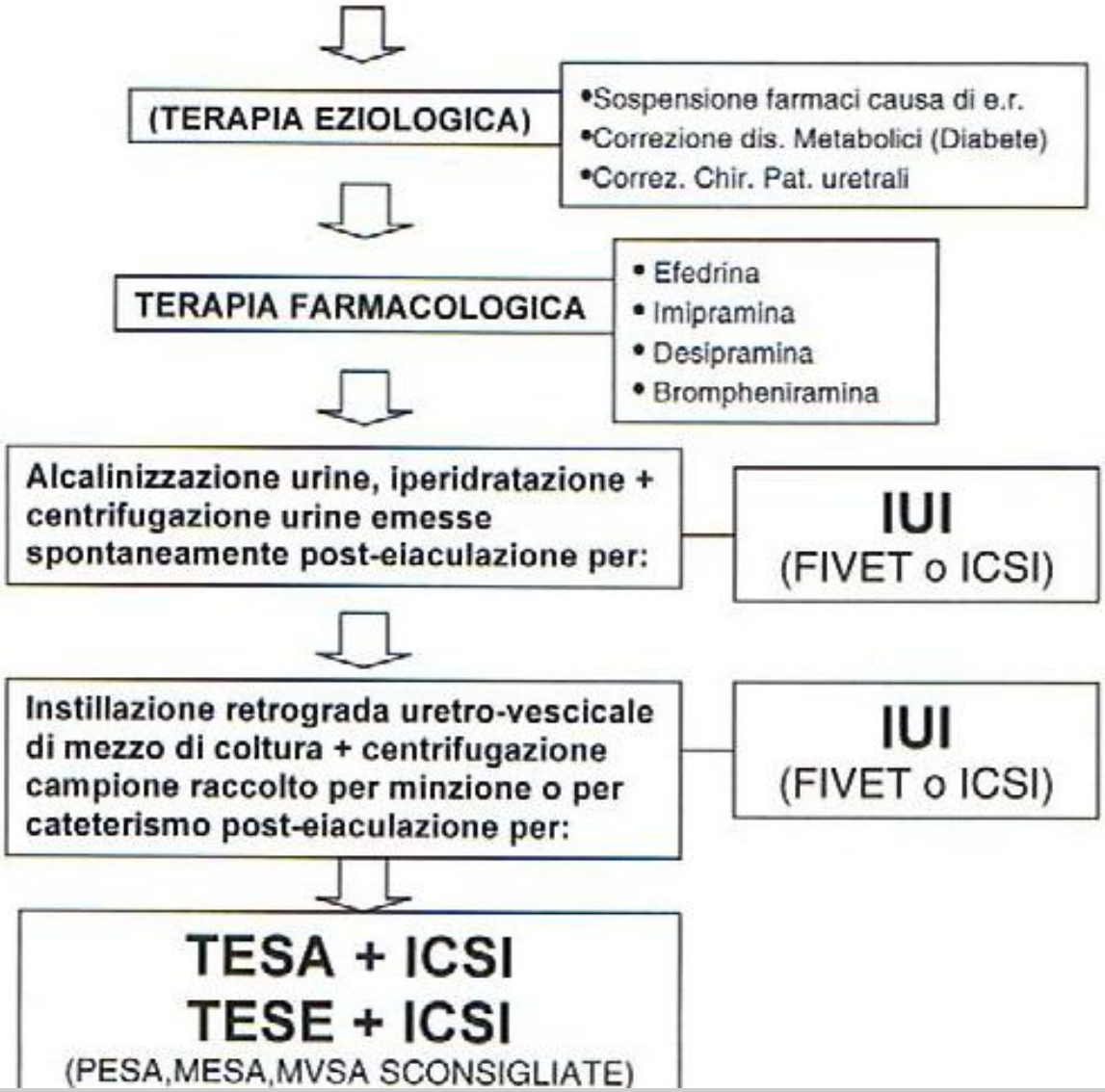
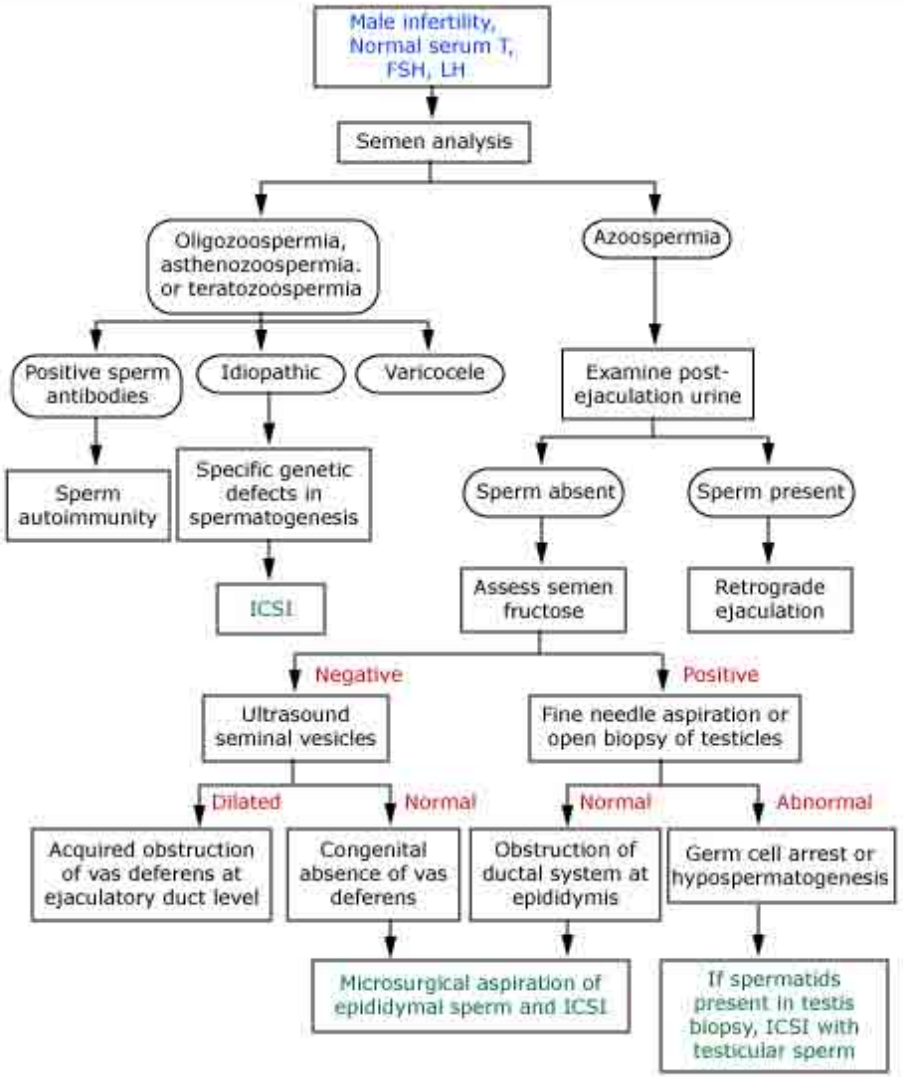
EIACULAZIONE RETROGRADA



Approach to diagnosis of male infertility in patients with normal serum hormone concentrations



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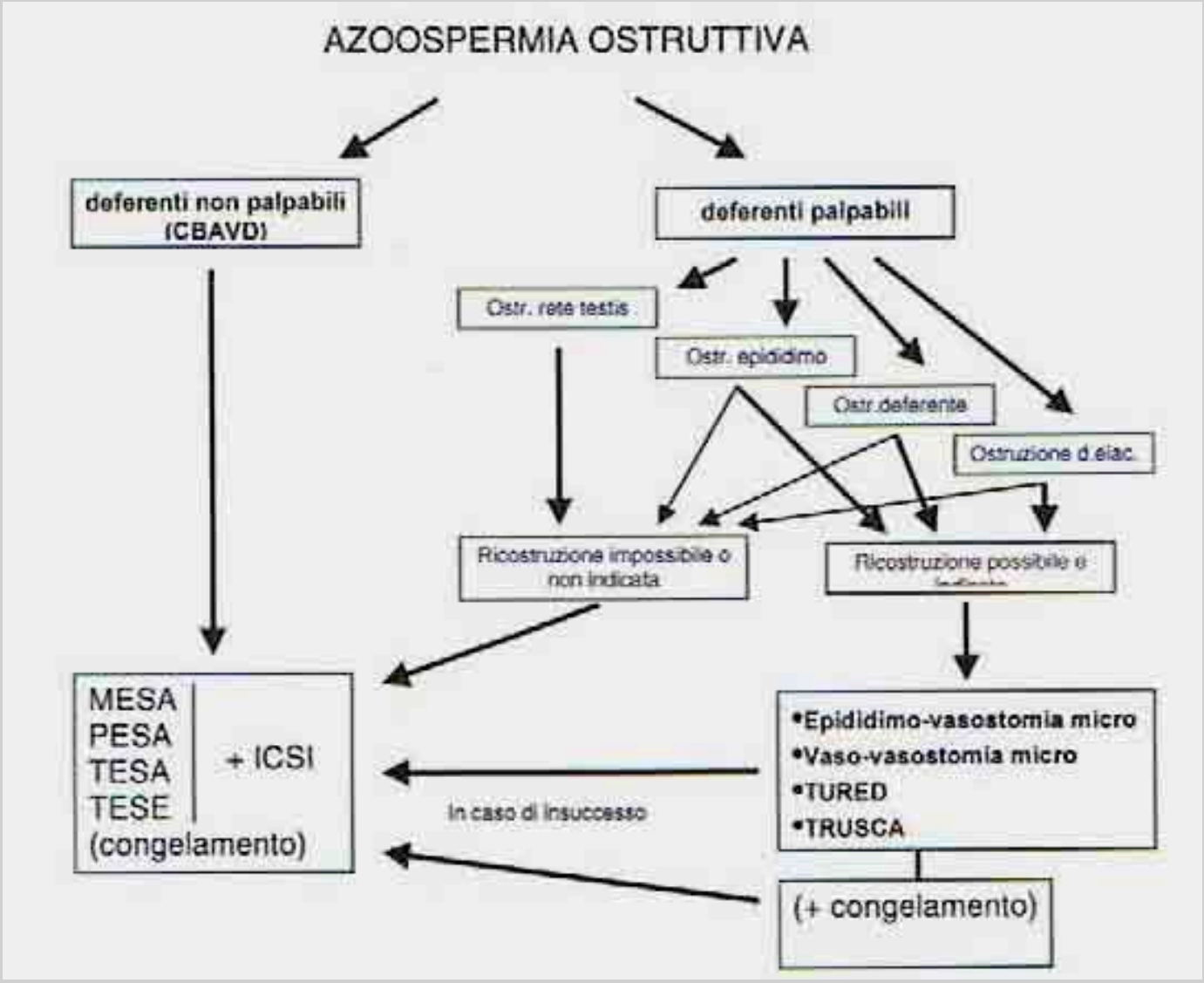
UpToDate


AZOOSPERMIA OSTRUTTIVA
deferenti non palpabili (CBAVD)
deferenti palpabili
Ostr. rete testis
Ostr. epididimo
Ostr.deferente
Ostruzione d.elac.
Ricostruzione impossibile o non indicata
Ricostruzione possibile o
MESA
PESA
TESA
TESE
(congelamento)
+ ICSI
In caso di insuccesso
•Epididimo-vasostomia micro
•Vaso-vasostomia micro
•TURED
•TRUSCA
(+ congelamento)

Empirical therapy which is unproven or ineffective for for male infertility

Hormones	Other
Androgens (mesterolone)	Alpha adrenergic agonists
Androgen withdrawal	Kallikrein
Gonadotropins*	Pentoxifylline
Gonadotropin-releasing hormone*	Vitamin E
Antiestrogens (clomiphene, tamoxifen)	Antibiotics
Aromatase inhibitor (testolactone, anastrazole, letrozole)	Corticosteroids
	Captopril
	Zinc
	Cooling of testes

* Both gonadotropins and gonadotropin-releasing hormone can be used for the specific treatment of hypogonadotropic hypogonadism.

PERCORSO GONADI 2

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INQUADRAMENTO
DELL'INFERTILITA' DI COPPIA

Partner femminile

CAUSE DI INFERTILITA' FEMMINILE
QUALE SPECIALISTA?

Cause ovariche	**ENDOCRINOLOGO**
Cause tubariche	GINECOLOGO
Cause uterine	GINECOLOGO
Endometriosi	GINECOLOGO
Fattori cervicali	GINECOLOGO

World Health Organization classification of anovulation

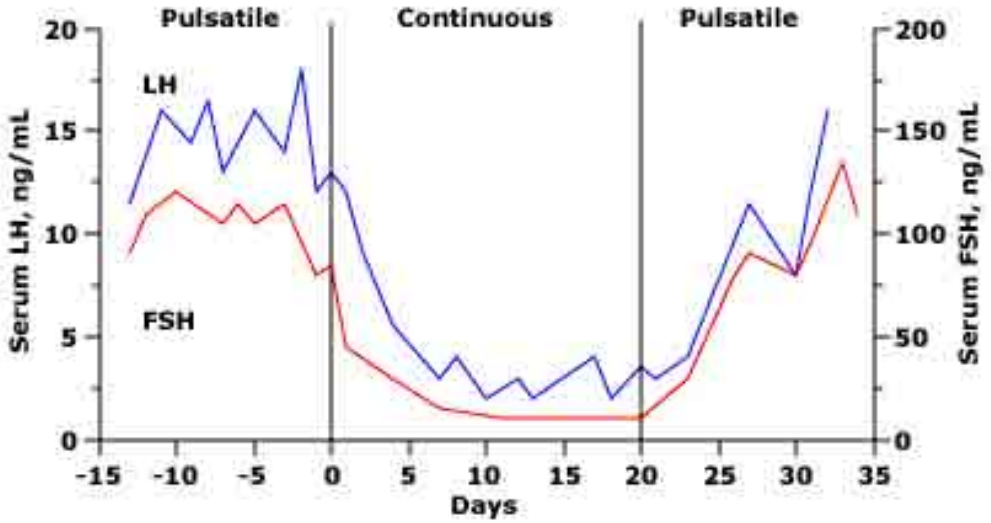
WHO class 1: Hypogonadotropic hypogonadal anovulation (hypothalamic amenorrhea)
These women have low or low-normal serum follicle-stimulating hormone (FSH) concentrations and low serum estradiol concentrations due to decreased hypothalamic secretion of gonadotropin-releasing hormone (GnRH) or pituitary unresponsiveness to GnRH.
WHO class 2: Normogonadotropic normoestrogenic anovulation
These women may secrete normal amounts of gonadotropins and estrogens. However, FSH secretion during the follicular phase of the cycle is subnormal. This group includes women with polycystic ovary syndrome (PCOS). Some ovulate occasionally, especially those with oligomenorrhea.
WHO class 3: Hypergonadotropic hypoestrogenic anovulation
The primary causes are premature ovarian failure (absence of ovarian follicles due to early menopause) and ovarian resistance (follicular form).
Hyperprolactinemic anovulation
These women are anovulatory because hyperprolactinemia inhibits gonadotropin and therefore estrogen secretion; they may have regular anovulatory cycles, but most have oligomenorrhea or amenorrhea. Their serum gonadotropin concentrations are usually normal.

UpToDate

CAUSE OVARICHE (WHO I) DI INFERTILITA'
TRATTAMENTO CON GnRH

✓ **GnRH** 2,5-10 µg e.v. OGNI 60-90'.
MONITORIZZAZIONE DELL'ANDAMENTO DEI CICLI.
LA SOMMINISTRAZIONE SOTTOCUTE RISULTA MENO EFFICACE.
GENERALMENTE SI OPTA PER LA STIMOLAZIONE CON GONADOTROPINE
✓rhFSH + rhLH (150-300 + 75-225 UI) O IN ALTERNATIVA hMG (150-300 UI) PER 10-15 GG FINO A SVILUPPO DI ALMENO UN FOLLICOLO DI 18mm, POI 10000 UI DI hCG

Importance of the pattern of GnRH secretion



Serum LH and FSH concentrations in an ovariectomized monkey. Pulsatile administration (given for six minutes every hour) of gonadotropin-releasing hormone (GnRH) maintains serum FSH and LH concentrations. In comparison, a continuous infusion of GnRH (middle panel) leads to rapid and reversible suppression of both LH and FSH release.

Data from: Belchetz PE, Plant TM, Nakai Y, et al. Hypophysial responses to continuous and intermittent delivery of hypopthalamic gonadotropin-releasing hormone. Science 1978; 202:631.

UpToDate

Multistep approach to treatment of anovulatory infertility associated with polycystic ovary syndrome

Step	Intervention	Cost	Risk of multiple gestation pregnancy
1	Weight loss (if baseline weight is elevated)	Low	Not increased
2	Clomiphene	Low	Modest increase in risk
3	Clomiphene plus dexamethasone*	Low	Modest increase in risk
4	FSH injections	Resource intensive	Markedly increased
5	Ovarian surgery	Resource intensive	Not increased
6	In vitro fertilization	Resource intensive	Potentially increased but controllable (eg, single embryo transfer)•

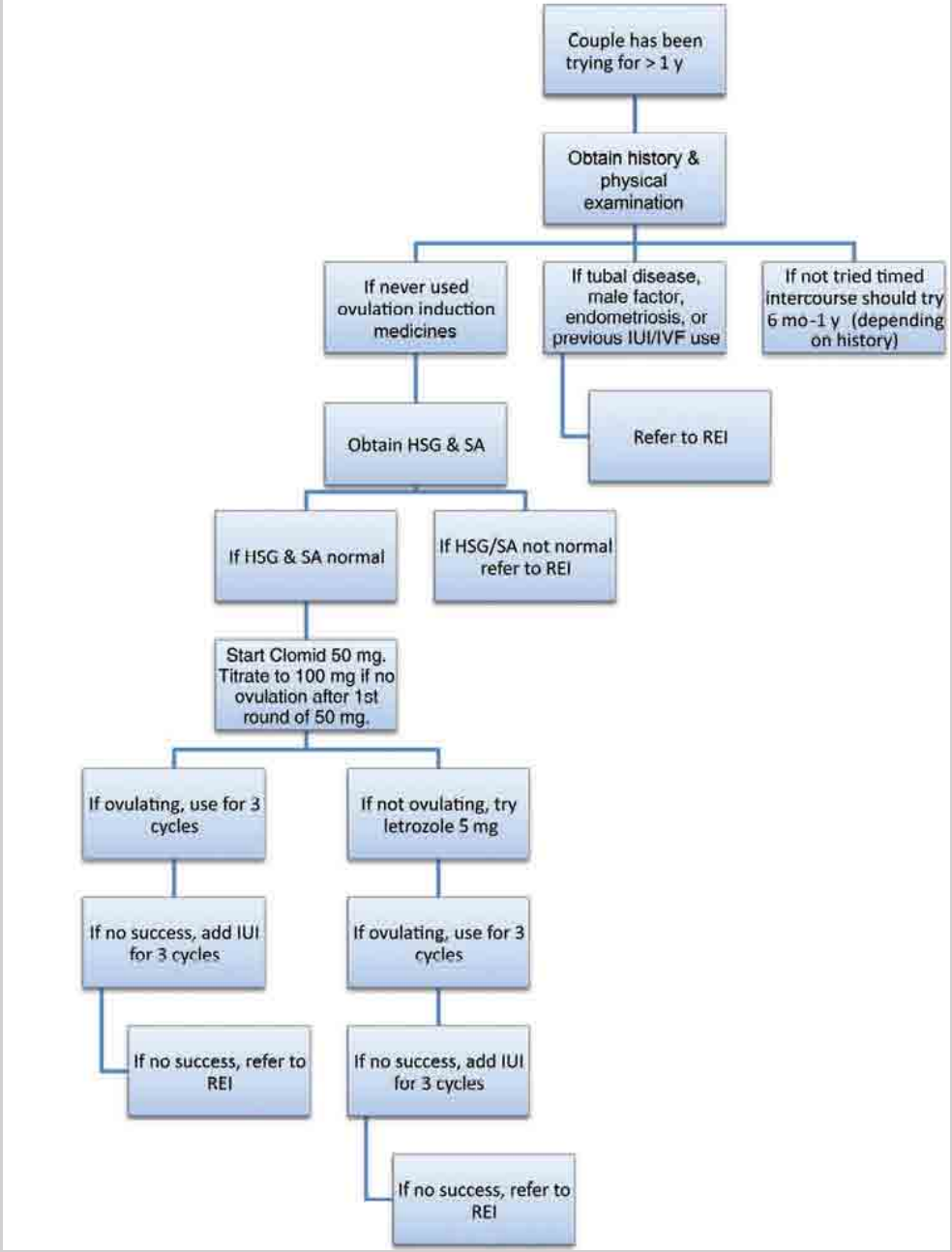
The initial steps emphasize interventions that are low cost and associated with a low risk of multiple gestation.

*Most clinicians go directly to FSH injections if clomiphene alone fails. However, the addition of dexamethasone is an alternative for those who value low cost and low risk of multiple gestation.

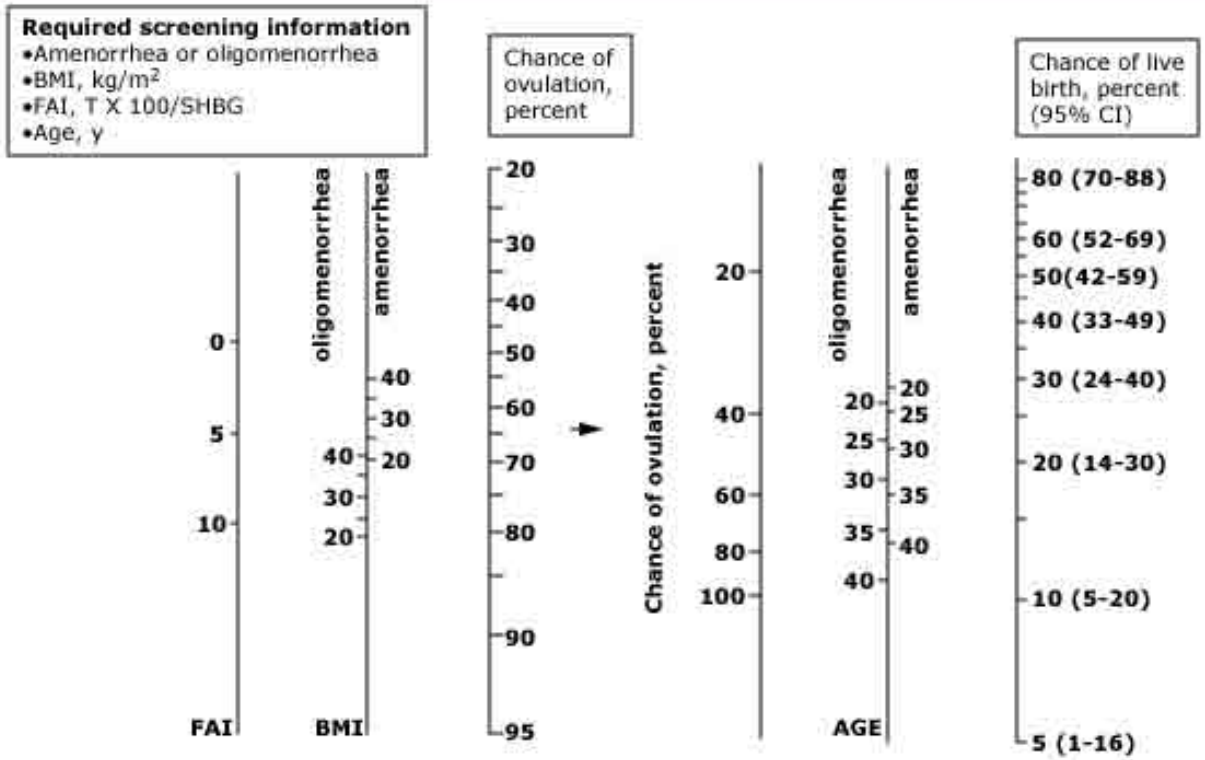
• This increased risk is dependent on the number of embryos transferred.

Courtesy of Robert L Barbieri, MD.

Oral Ovulation Induction Treatment Algorithm



Live birth following clomiphene citrate



A two-step nomogram predicting chances for live birth following clomiphene citrate on the basis of initial screening characteristics.
FAI: free androgen index.

CAUSE OVARICHE (WHO II) DI INFERTILITA'

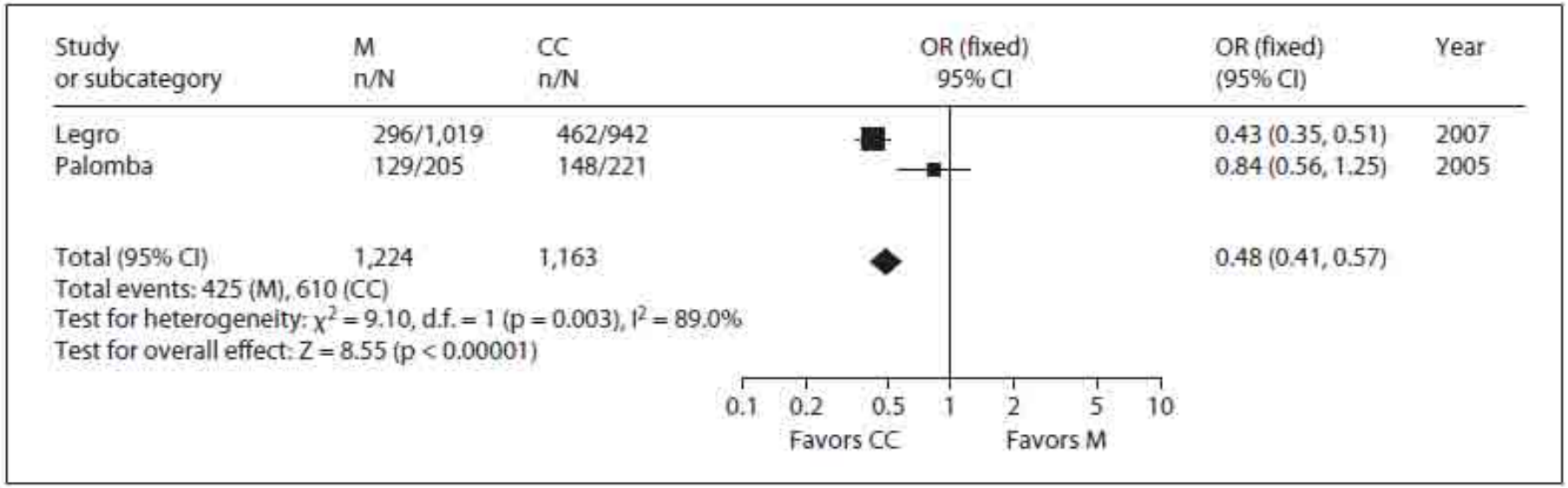


Fig. 4. CC vs. M: ovulation. When ovulation is the primary endpoint, CC alone performed significantly better than M alone. $p < 0.00001$.

CAUSE OVARICHE (WHO II) DI INFERTILITA'

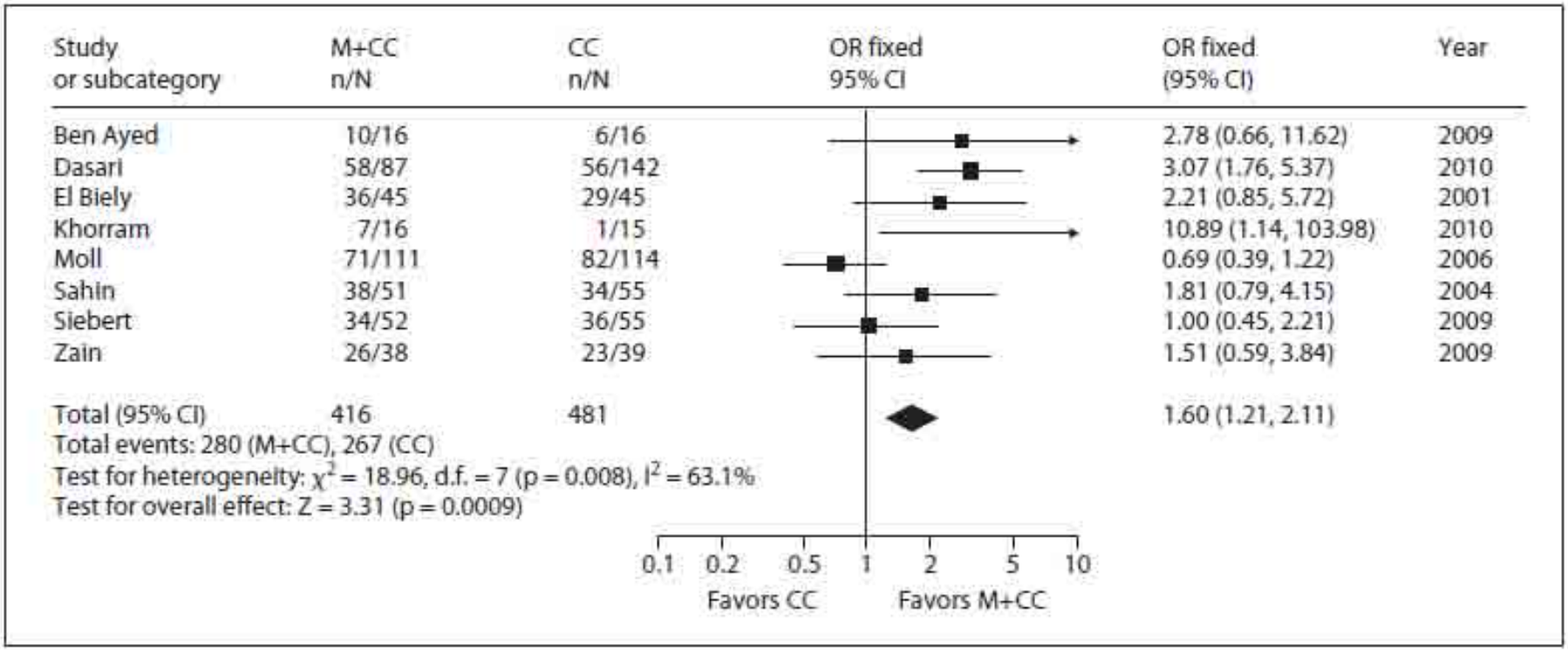


Fig. 5. M+CC vs. CC: ovulation. Ovulation was significantly better with the combination (CC+M) compared with CC alone. $p < 0.00001$.

CAUSE OVARICHE (WHO II) DI INFERTILITA'

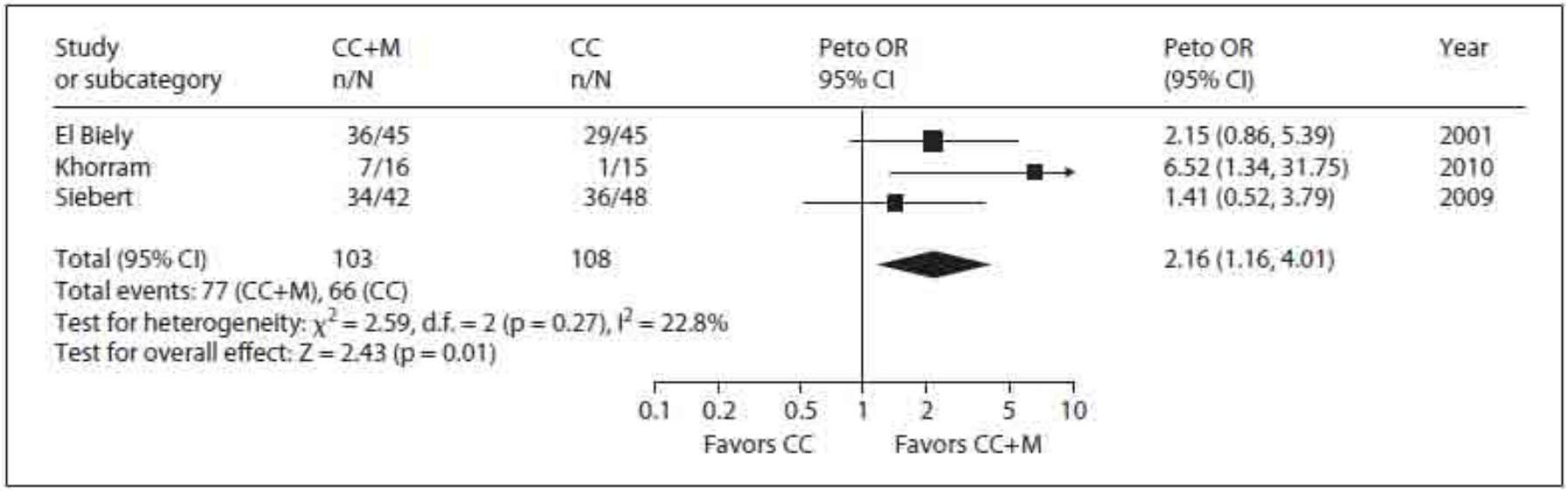


Fig. 6. CC+M vs. CC in obese women – BMI >25: ovulation. Ovulation was significantly better with CC+M when compared with CC alone in the obese patients. p = 0.01.

CAUSE OVARICHE (WHO II) DI INFERTILITA'

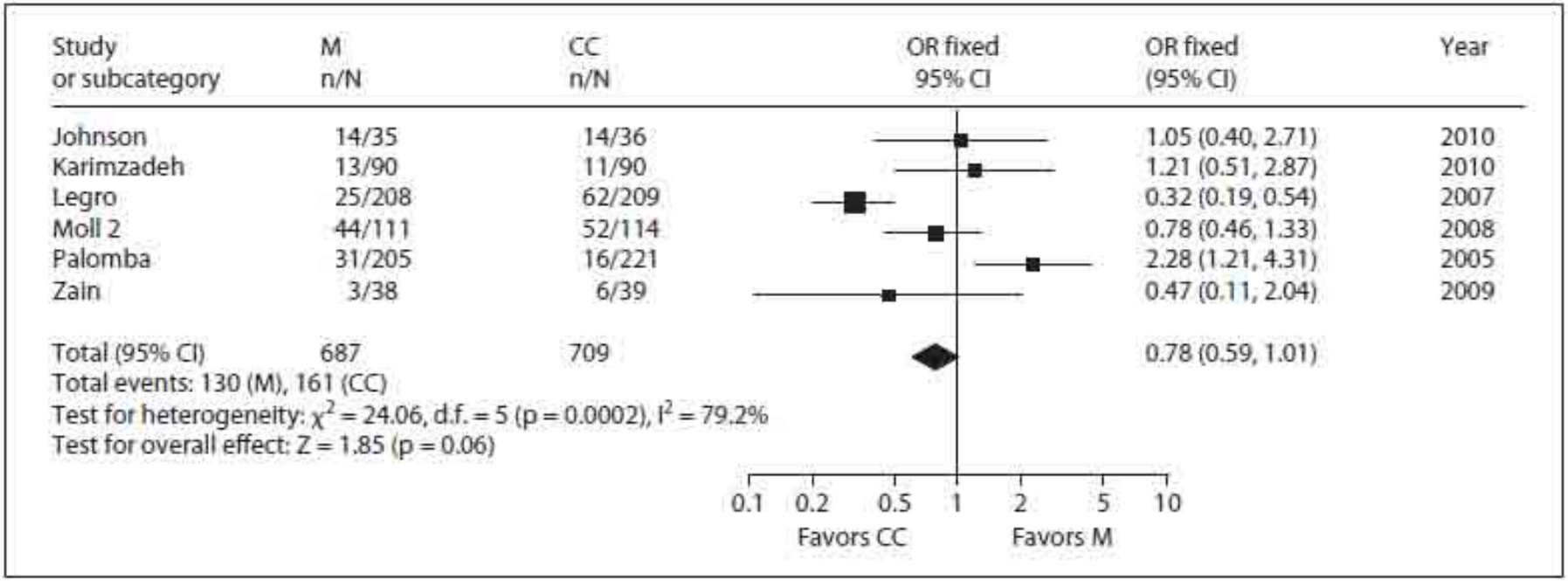


Fig. 7. CC vs. M: pregnancy. No significant difference between the two groups. p = 0.76.

CAUSE OVARICHE (WHO II) DI INFERTILITA'

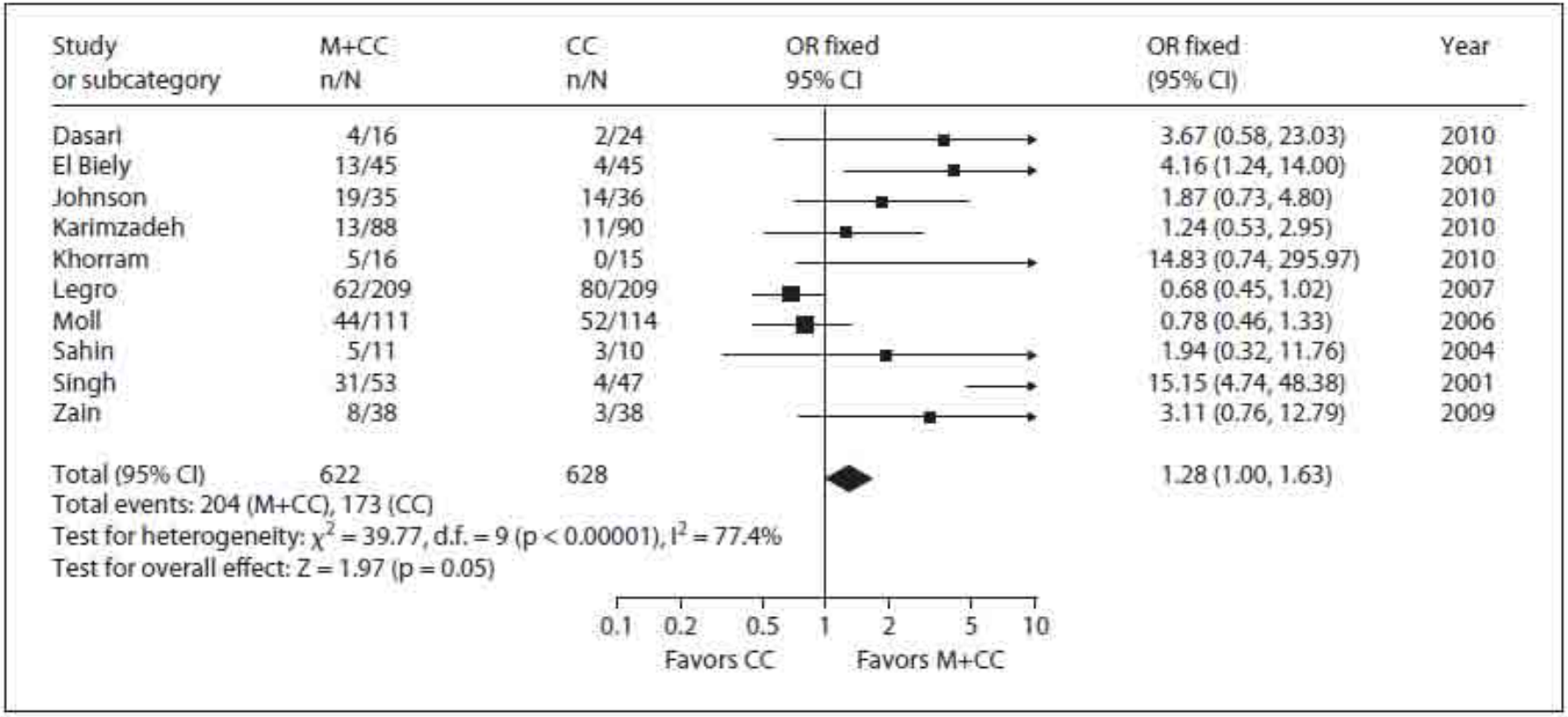


Fig. 8. M+CC vs. CC: pregnancy. Pregnancy rate was significantly better with the combination (CC+M) compared with CC alone. p = 0.05.

CAUSE OVARICHE (WHO II) DI INFERTILITA'

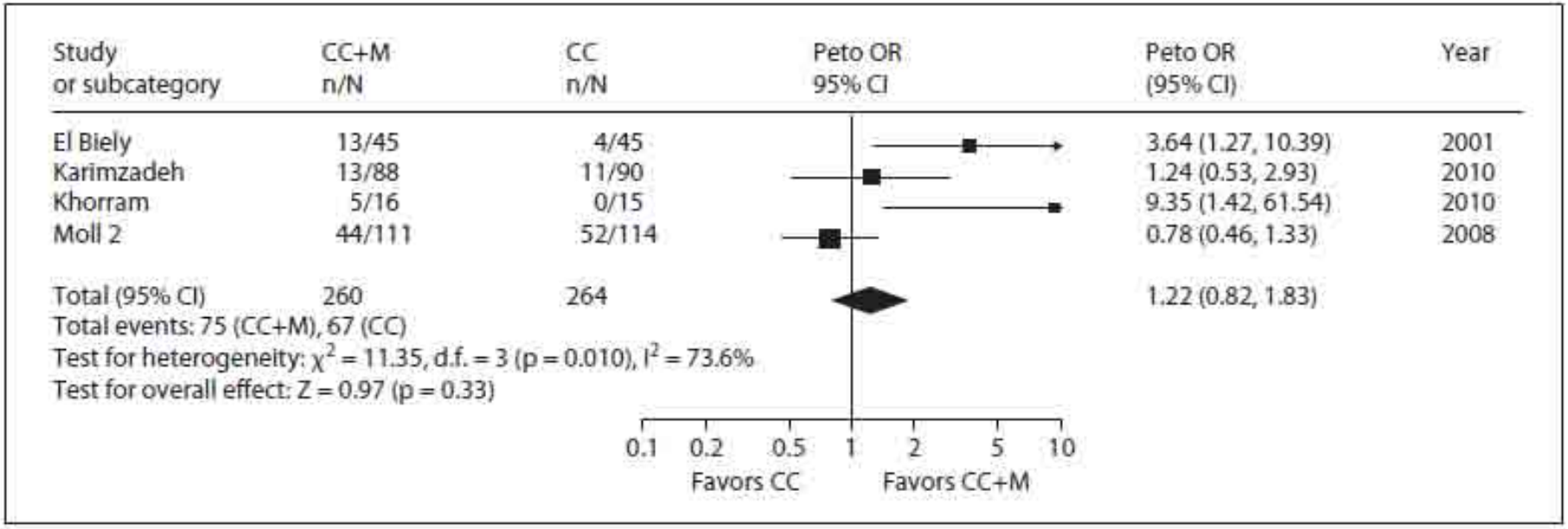


Fig. 9. CC+M vs. CC in obese women – BMI >25: pregnancy. No significant difference between the two groups. p = 0.33.

CAUSE OVARICHE (WHO II) DI INFERTILITA'

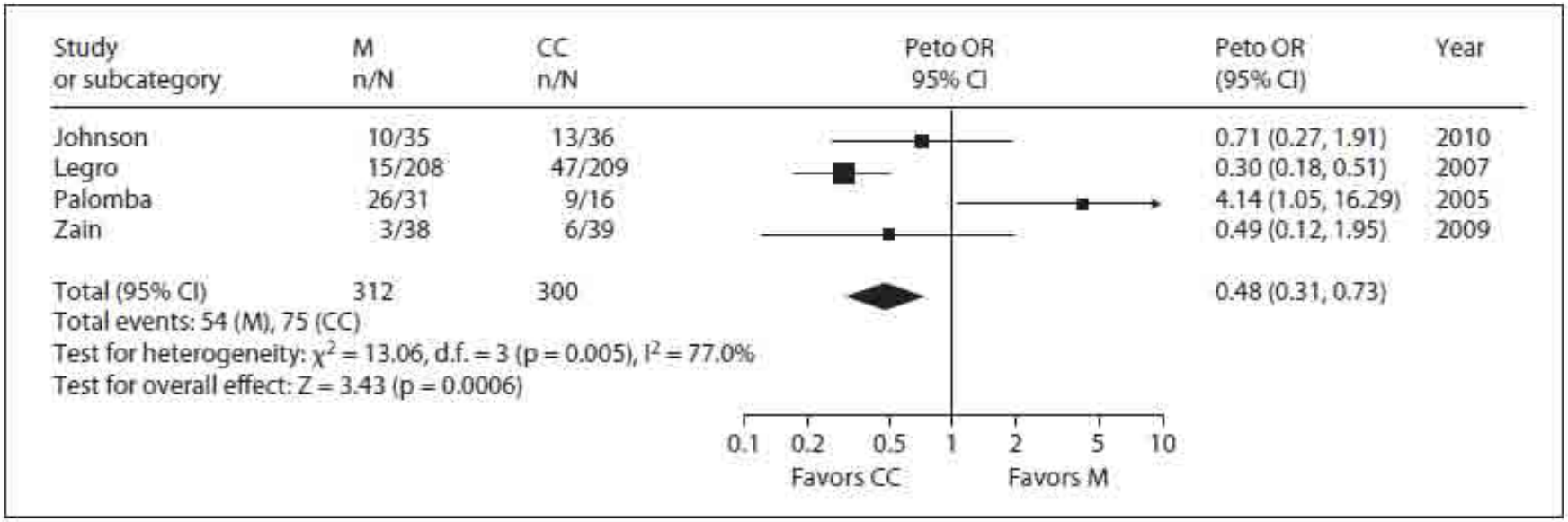


Fig. 2. CC vs. M: live birth. Better live birth rate with CC alone when compared with M alone. p = 0.0006.

CAUSE OVARICHE (WHO II) DI INFERTILITA'

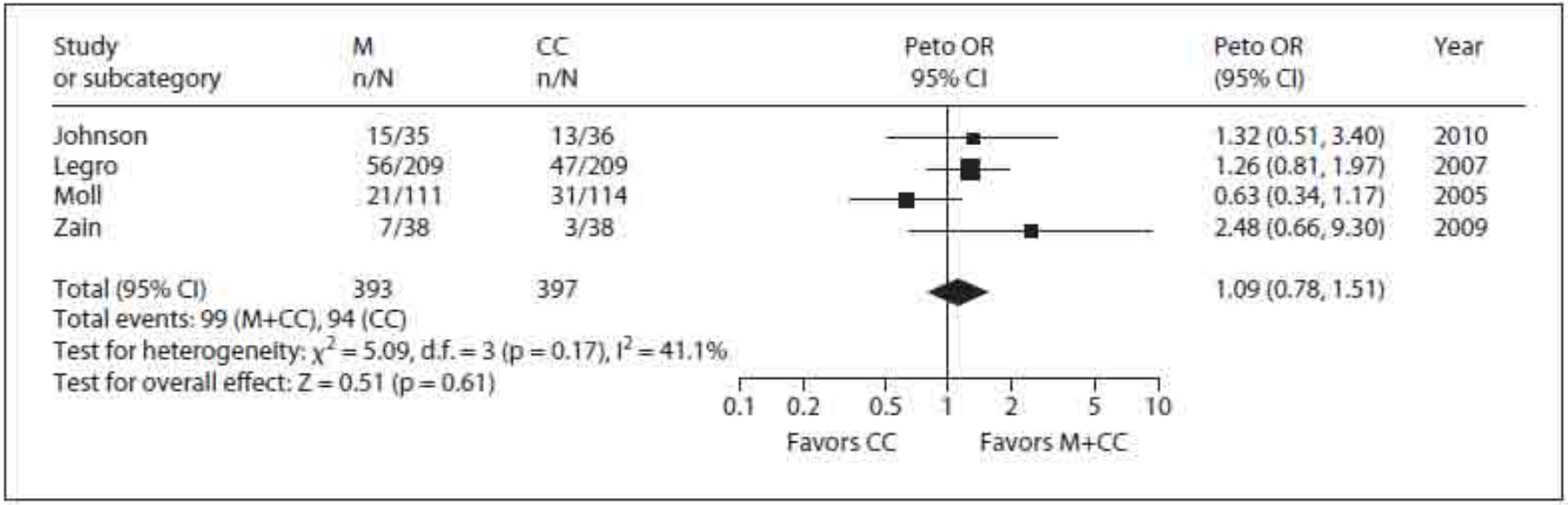


Fig. 3. M+CC vs. CC: live birth. No significant difference between the two groups. p = 0.61.

CAUSE OVARICHE (WHO II) DI INFERTILITA'

4 D-chiro-inositol versus placebo or no treatment

Although two trials were included (Gerli 2003; Nestler 1999), the number of women in the analysis remained small. Furthermore, one of the trials (Gerli 2003) reported analysable data for only one outcome of interest (ovulation rate). It would be difficult to make any conclusions based on the current findings.

6 Pioglitazone versus placebo or no treatment

Data were not available for primary outcomes, but were available for some secondary outcomes, including menstrual frequency and anthropometric, endocrine and metabolic outcomes.

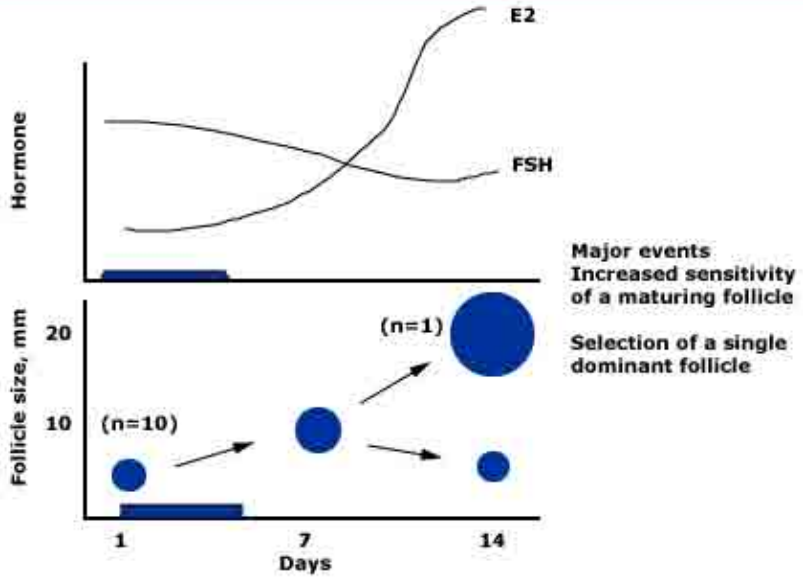
Pioglitazone improved the menstrual pattern (2 RCTs, 70 participants; OR 8.88, 95% CI 2.35 to 33.61; I^2 = 0%, Analysis 6.1).

There were no effects on anthropometric outcomes (BMI, WHR: Analysis 6.2; Analysis 6.3), endocrine outcomes (testosterone, SHBG: Analysis 6.4; Analysis 6.5;) or metabolic outcomes (fasting insulin: Analysis 6.6)

CAUSE OVARICHE (WHO I E WHO II) DI INFERTILITA'
INDICAZIONI AL TRATTAMENTO CON GONADOTROPINE

- ✓ PAZIENTI NORMOGONADOTROPE CHE NON HANNO RISPOSTO AL CLOMIFENE
- ✓ PAZIENTI IPOGONADOTROPE COME SECONDA LINEA DI TRATTAMENTO

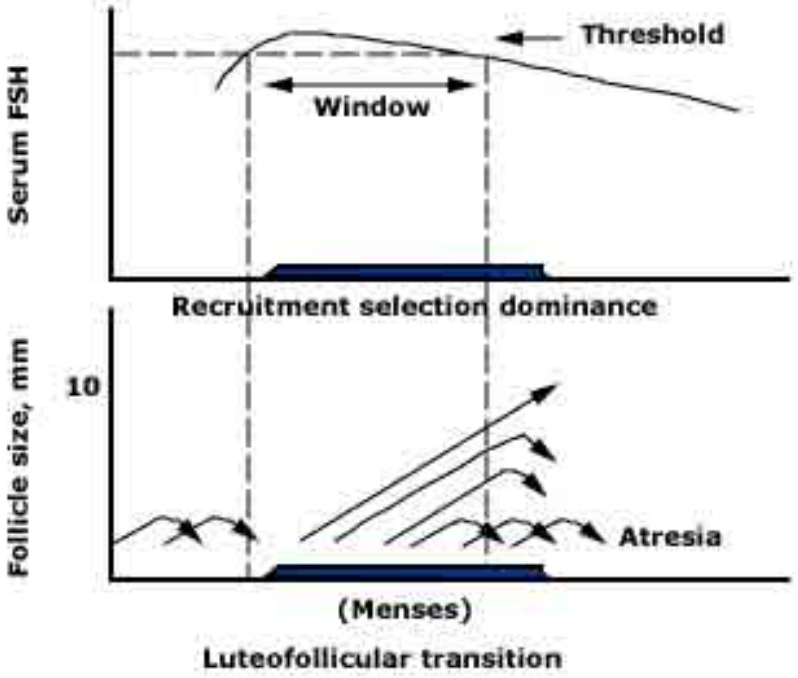
Human follicle development



Schematic representation of human follicle development during the follicular phase of the menstrual cycle. There are two major events in this process: increased sensitivity of a maturing follicle; and selection of a single dominant follicle. In spontaneous cycles, this is achieved at the beginning of the cycle by a transient increase in serum FSH concentrations above some threshold value; the concentrations then decrease, preventing more than one follicle from undergoing preovulatory development.

Fauser, BC, Van Hevsdeau, AM, et al. Manipulation of human ovarian function: Physiological concepts and clinical consequences. Endocr Rev 1997; 18:71.

FSH threshold and follicular development



The intercycle rise in serum FSH concentrations exceeds the threshold for recruitment of follicles for further development. The number of follicles recruited is determined by the time ("window") in which the serum FSH is above the threshold at which recruitment occurs.

UpToDate

CAUSE OVARICHE (WHO I E WHO II) DI INFERTILITA'

Nota 74

- Determinazione 27 aprile 2010 (GU 17 maggio 2010, n. 113): modifica alla nota AIFA 74 di cui alla determinazione 23 febbraio 2007, e successivo

- Comunicato di rettifica relativo all'estratto della determinazione del 27 aprile 2010 recante la modifica della nota AIFA 74 (GU 16 giugno 2010, n 138

La prescrizione a carico del SSN, su diagnosi e piano terapeutico di strutture specialistiche, secondo modalità adottate dalle Regioni e dalle Province Autonome di Trento e Bolzano, è limitata alle seguenti condizioni:

- **trattamento dell'infertilità femminile:in donne di età non superiore ai 45 anni con valori di FSH, al 3° giorno del ciclo, non superiori a 30 mUI/ml**

CAUSE OVARICHE (WHO II) DI INFERTILITA'
TRATTAMENTO CON GONADOTROPINE

Roma,
9-11 novembre 2012

- ✓ **PROTOCOLLO CONVENZIONALE IN STEP-UP**
  150-225 UI DI FSH i.m. PER 7GG CON INCREMENTI DI 75UI AD INTERVALLI DI 7 GG

TASSO CONCEPIMENTO 46%
IPERSTIMOLAZIONE 5%
GRAVIDANZE MULTIPLE 34%

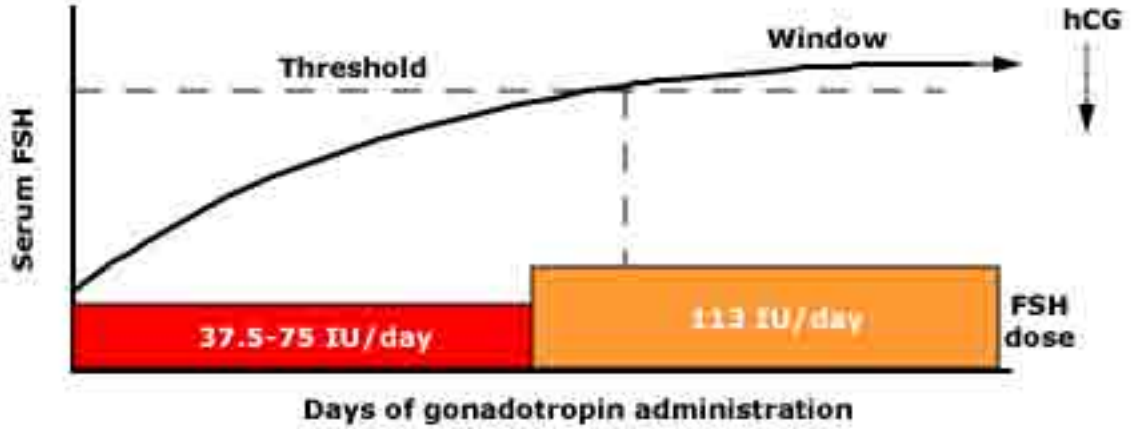
CAUSE OVARICHE (WHO II) DI INFERTILITA'
TRATTAMENTO CON GONADOTROPINE

✓**PROTOCOLLO A BASSE DOSI IN STEP-UP**

50 UI DAL 1° GIORNO PER 14 GG O DOSE PERSONALIZZATA IN GRADO DI INDURRE RECLUTAMENTO. IN ASSENZA DI RISPOSTA INCREMENTO DEL 30% DELLA DOSE
LA STIMOLAZIONE PUO' ESSERE PROTRATTA ANCHE PER 5 SETT PER IDENTIFICARE LA DOSE DI FSH IN GRADO DI INDURRE LA CRESCITA DI 1-2 FOLLICOLI, POI SI MANTIENE LO STESSO DOSAGGIO FINO ALLA SOMMINISTRAZIONE DI 5000-10000 UI DI hCG

TASSO CONCEPIMENTO 48%
IPERSTIMOLAZIONE 0,3%
GRAVIDANZE MULTIPLE 7%

Step-up protocol for ovulation induction



Schematic representation of the low-dose, step-up protocol of gonadotropin administration for ovulation induction. The initial subcutaneous or intramuscular dose of FSH is 37.5 to 75 IU/day; the dose is increased only if, after 14 days, no response is documented on ultrasonography and serum estradiol monitoring. Increments of 37.5 IU then are given at weekly intervals up to a maximum of 225 IU/day. Detection of an ovarian response is an indication to continue the current dose until hCG can be given to stimulate ovulation.

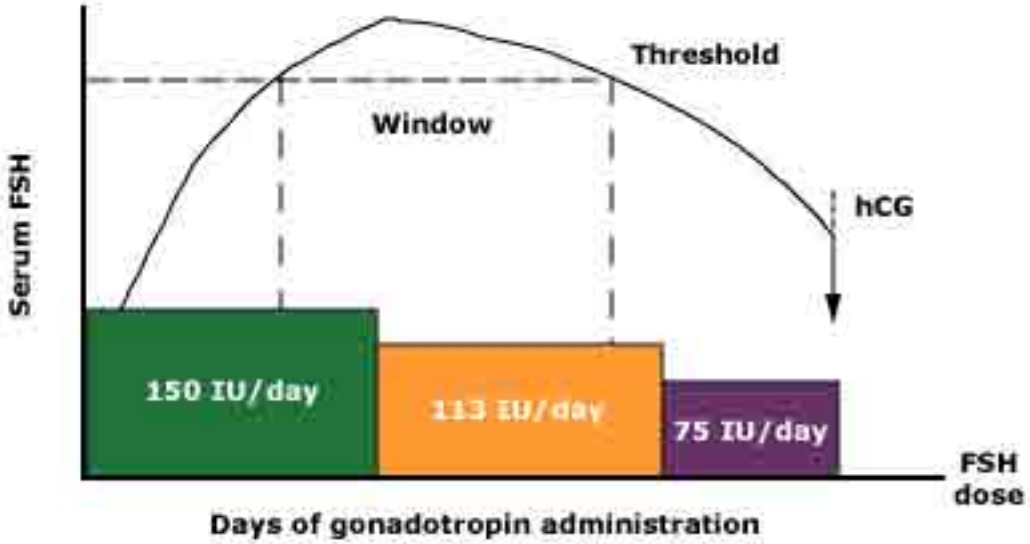
CAUSE OVARICHE (WHO II) DI INFERTILITA'
TRATTAMENTO CON GONADOTROPINE

✓**PROTOCOLLO A BASSE DOSI IN STEP-DOWN**

150 UI DAL 1° GIORNO POI RIDOTTA A 100 UI QUANDO 1 FOLLICOLO HA RAGGIUNTO LA DOMINANZA, DOPO 3 GG ULTERIORE RIDUZIONE A 5O FINO ALLA SOMMINISTRAZIONE DI 5000-10000 UI DI hCG

TASSO CONCEPIMENTO 18%
IPERSTIMOLAZIONE 29%
GRAVIDANZE MULTIPLE 1%

Step-down protocol for ovulation induction



Schematic representation of the step-down protocol of gonadotropin administration, which is designed to bring about development of single follicles. This regimen mimics more closely the physiology of normal cycles. Therapy with FSH at a dose of 150 IU/day is started shortly after spontaneous or progesterone-induced bleeding and continued until a dominant follicle (>10 mm) is seen on transvaginal ultrasonography. The dose is then decreased to 112.5 IU/day followed by a further decrease to 75 IU/day, which is continued until human chorionic gonadotropin (hCG) is administered to induce ovulation.

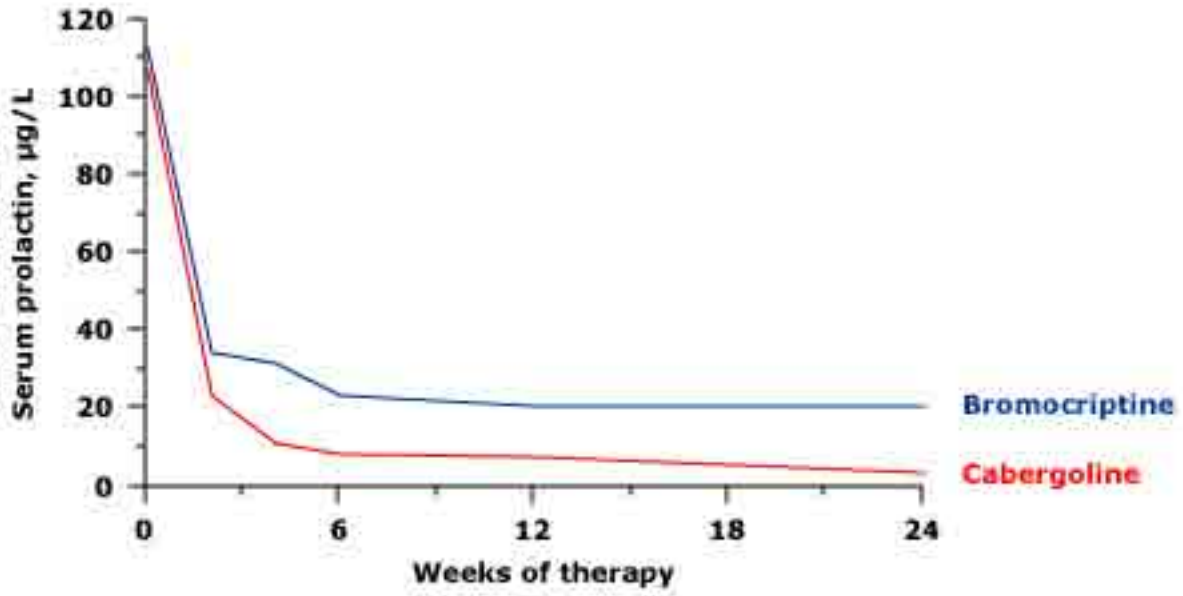
CAUSE OVARICHE (WHO II) DI INFERTILITA'
TRATTAMENTO CON GONADOTROPINE

✓**PROTOCOLLO A BASSE DOSI A GG ALTERNI**

50-100 UI DAL 1° GIORNO A GG ALTERNI

FINO ALLA SOMMINISTRAZIONE DI 5000-10000 UI DI hCG

Dopamine agonist drugs lower serum prolactin concentrations in lactotroph adenoma (prolactinoma)



Serum prolactin concentrations in women with hyperprolactinemic amenorrhea treated with bromocriptine and cabergoline. Both drugs lowered serum prolactin concentrations into the normal range (upper limit of normal equals 20 mcg/L).

Data from: Webster J, Piscitelli MD, Polli A, et al. A comparison of cabergoline and bromocriptine in the treatment of hyperprolactinemic amenorrhea. Cabergoline Comparative Study Group. N Engl J Med 1994; 331:904.

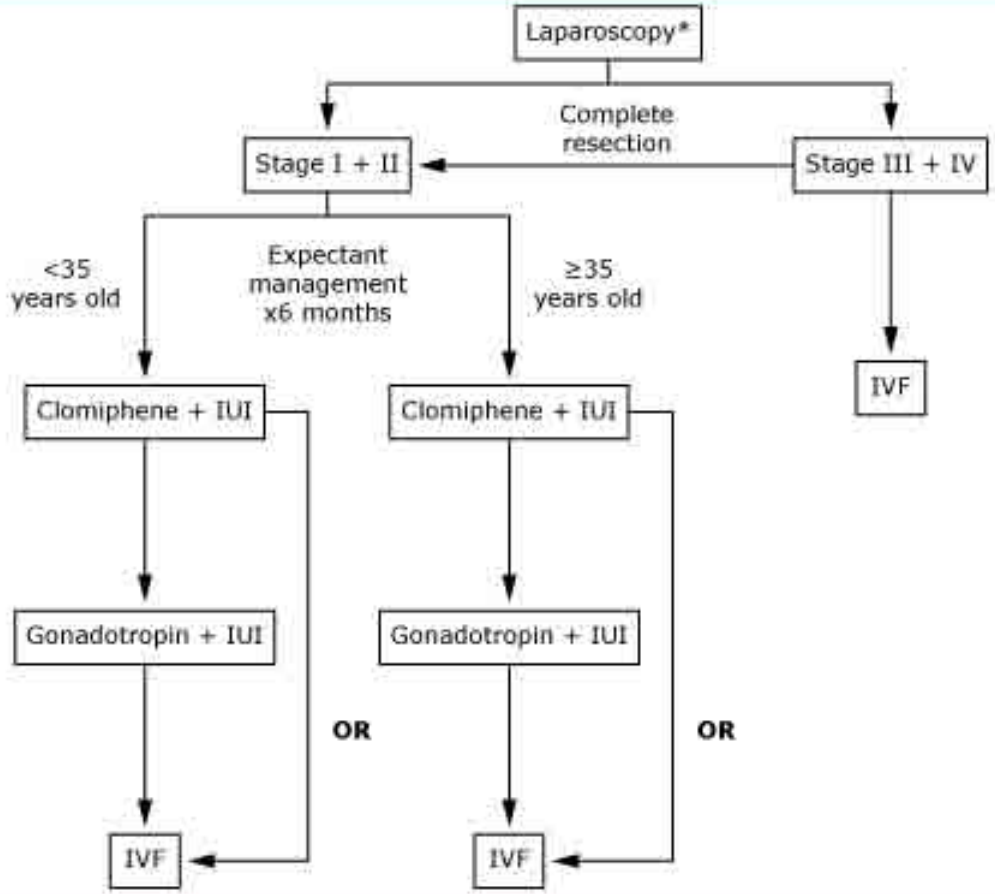
Approximate ovulation and pregnancy rates following ovulation induction

Treatment	Ovulation rate percent	Cumulative pregnancy rate percent
Clomiphene	80	50
Gonadotropins	72	50
Pulsatile GnRH*	90	80
Dopamine agonists•	80	70

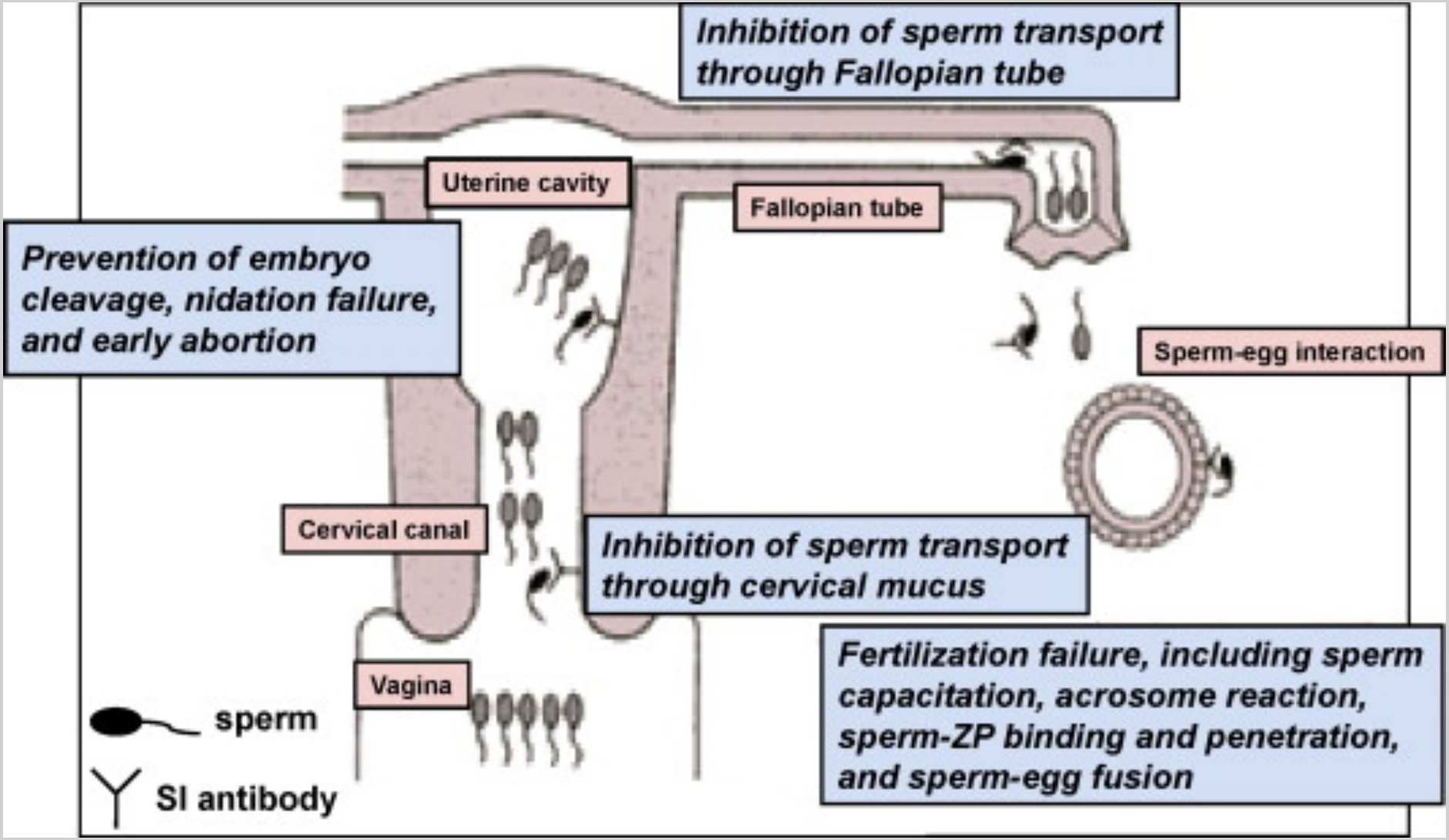
* Indicated only for women with hypogonadotropic hypogonadal anovulation (WHO class 1).
• Indicated only for women with hyperprolactinemia-induced anovulation.

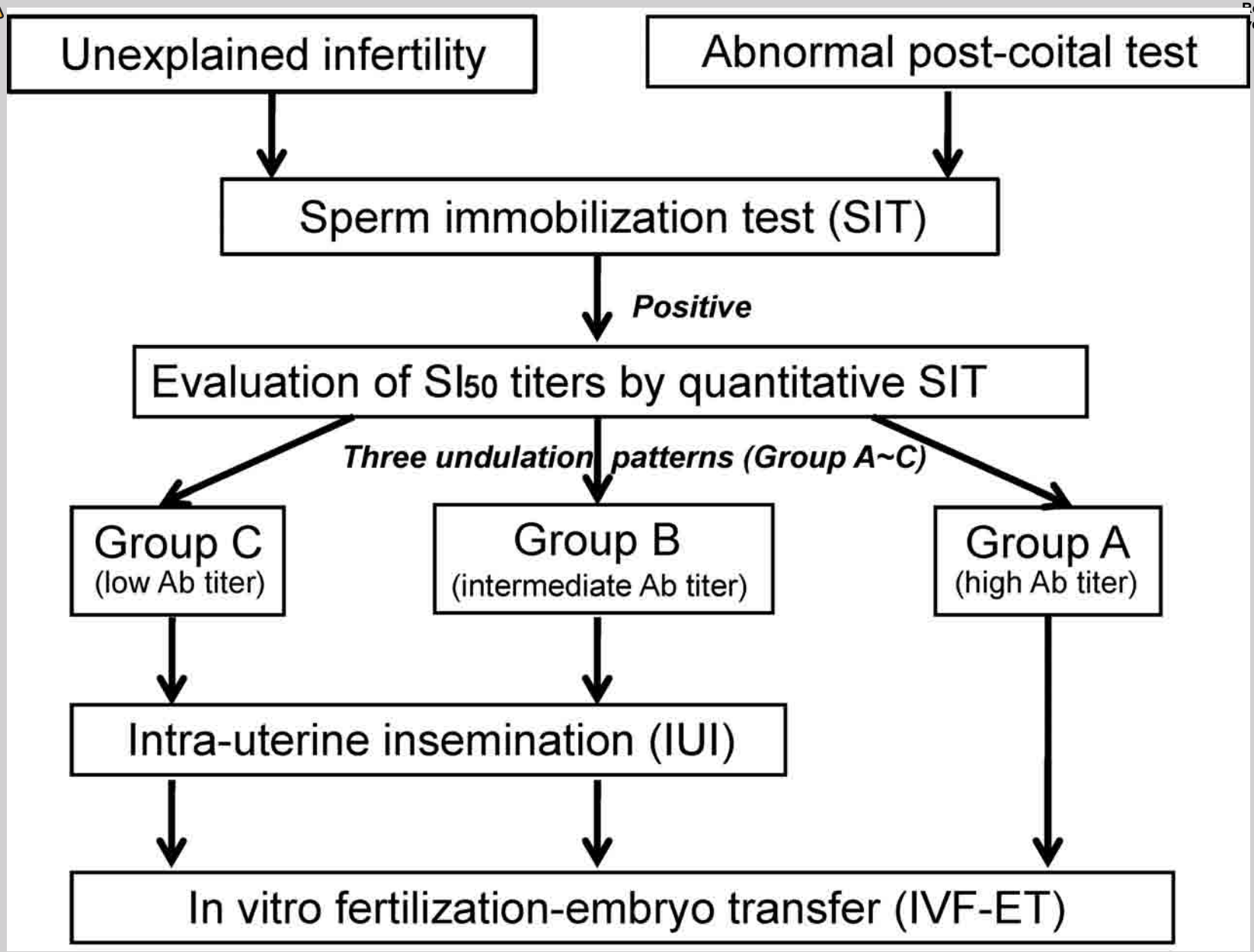
UpToDate

Flow for management of infertility in women with endometriosis

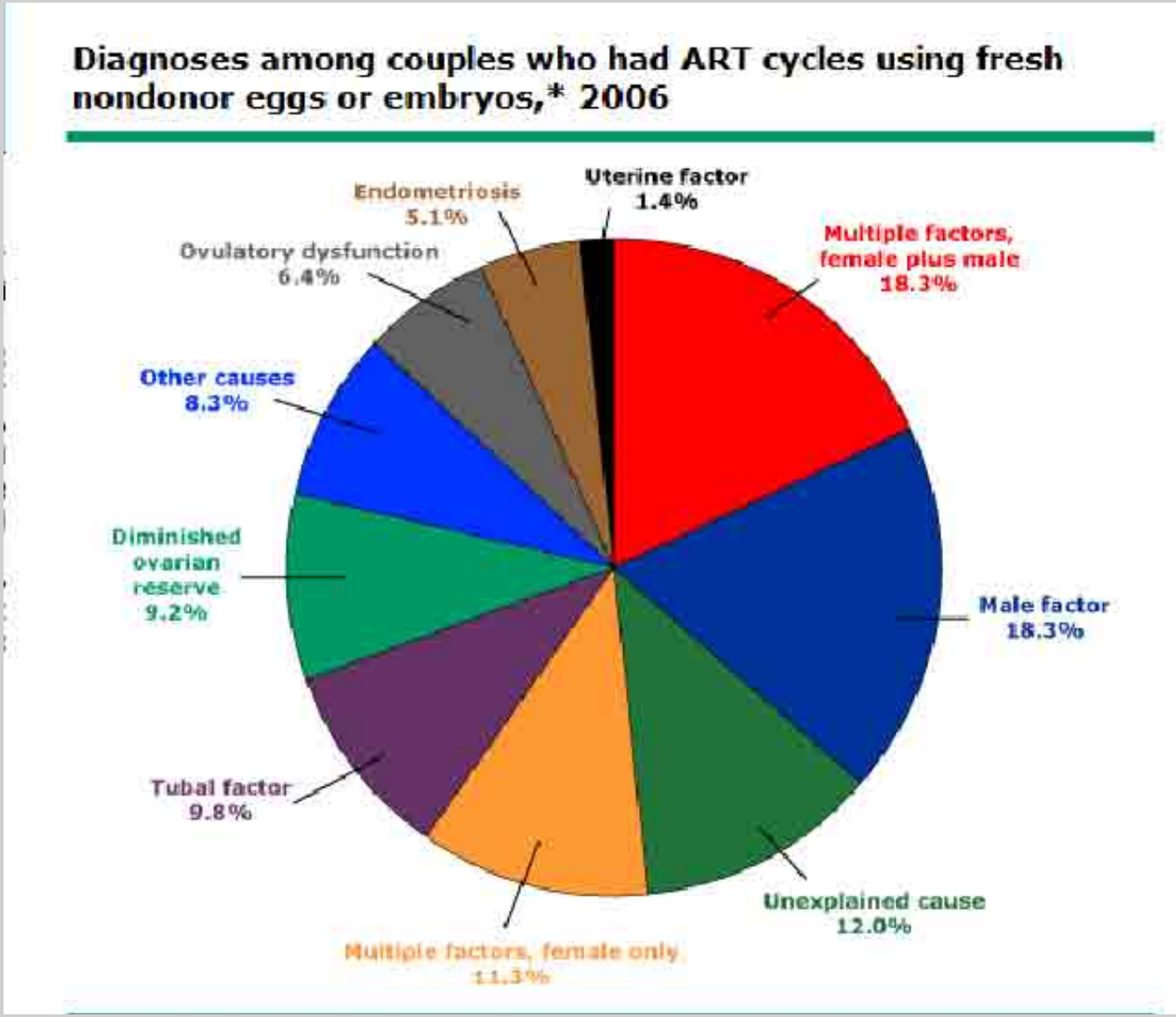


IVF = in vitro fertilization
IUI = intrauterine insemination
x6 months = for six months
stages refer to stages of endometriosis
* Laparoscopy may be remote from time of attempting pregnancy.


Inhibition of sperm transport through Fallopian tube
Uterine cavity
Fallopian tube
Prevention of embryo cleavage, nidation failure, and early abortion
Sperm-egg interaction
Cervical canal
Inhibition of sperm transport through cervical mucus
Vagina
Fertilization failure, including sperm capacitation, acrosome reaction, sperm-ZP binding and penetration, and sperm-egg fusion
sperm
SI antibody


Unexplained infertility
Abnormal post-coital test
Sperm immobilization test (SIT)
Positive
Evaluation of SI50 titers by quantitative SIT
Three undulation patterns (Group A~C)
Group C
(low Ab titer)
Group B
(intermediate Ab titer)
Group A
(high Ab titer)
Intra-uterine insemination (IUI)
In vitro fertilization-embryo transfer (IVF-ET)

TECNICHE DI FECONDAZIONE ASSISTITA - ART

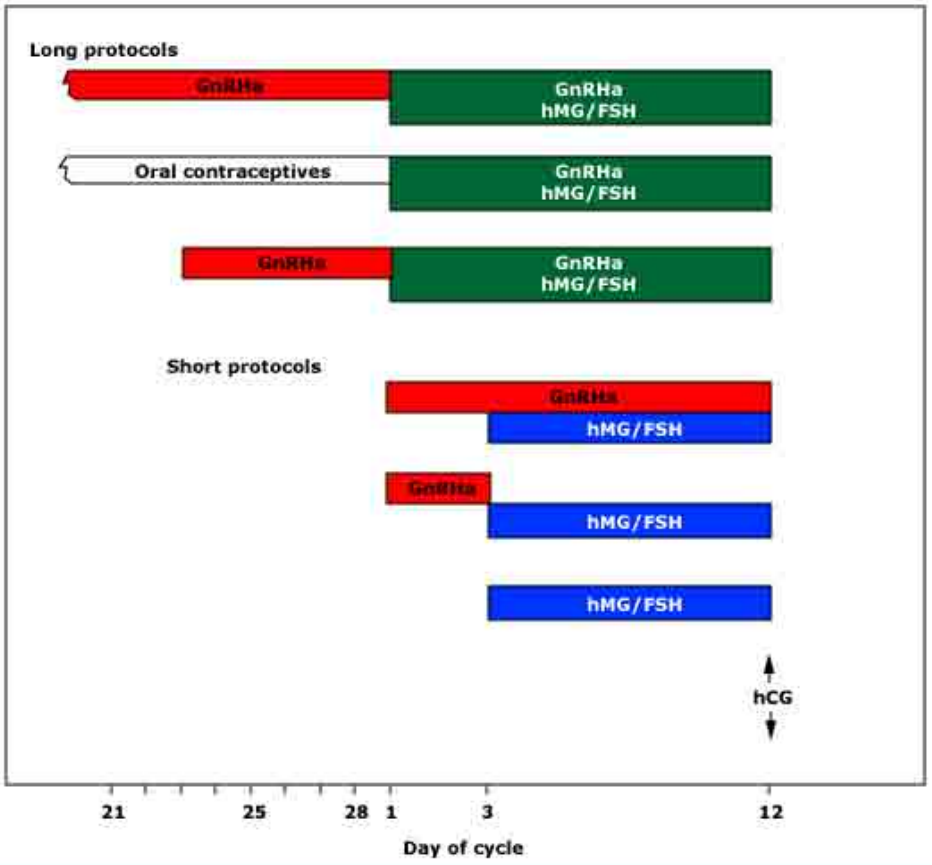


Assisted reproductive technologies

In vitro fertilization (IVF)
Aspiration of one or more oocytes from ovarian follicles, fertilization in vitro, and then transfer of the embryo(s) into the uterus. This is the most common procedure using assisted reproductive technology.
Intracytoplasmic sperm injection (ICSI) is a specialized technique for couples with severe sperm abnormalities. It is performed in conjunction with IVF whereby fertilization is accomplished by injecting a single sperm directly into the egg.
Gamete intrafallopian transfer (GIFT)
A laparoscope is used to aspirate one or more mature oocytes from ovarian follicles and then transfer the oocytes and sperm to the fallopian tube.
GIFT, although more invasive than IVF, may be an appropriate choice in patients who, for religious or personal reasons, do not wish to have embryos in the laboratory. It is also appropriate for those who have failed donor insemination or require laparoscopy for other reasons. The success rate is similar to those with IVF.
Zygote intrafallopian transfer (ZIFT) or tubal embryo transfer (TET)
This procedure involves placement of fertilized eggs (zygotes) or embryos into the fallopian tube.
ZIFT is analogous to GIFT in that laparoscopy is needed to place the zygotes in the fallopian tubes. Whereas overall success rates are similar to IVF, ZIFT may offer some advantages to patients with difficult trans-cervical embryo transfer, uterine abnormalities (such as those caused by DES exposure), or recurrent failture with standard IVF

Adapted from Meldrum, DR. Assisted Reproductive Technology: Clinical Aspects. In: Essentials of Reproductive Medicine. Hillier, SG, Kitchener, HC, Neilson, JP (eds) WB Saunders, Philadelphia,1996.

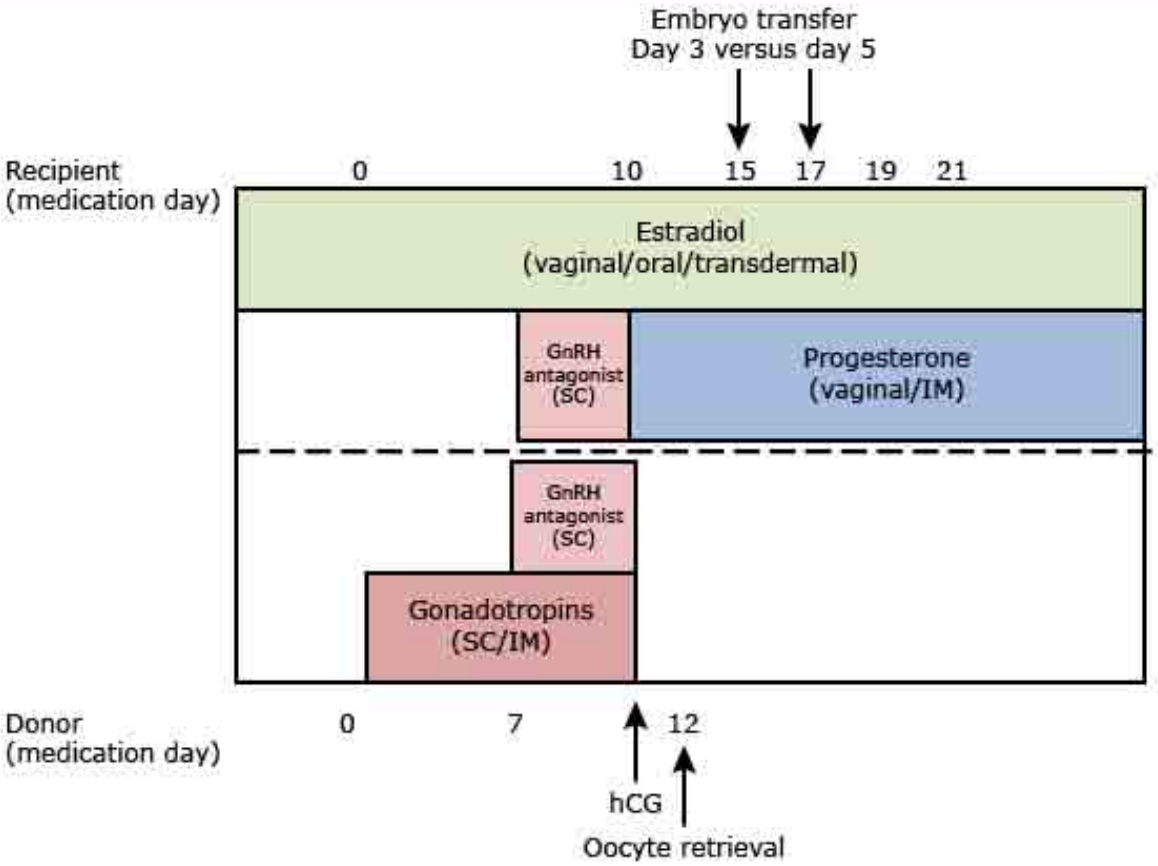
Examples of different approaches to ovarian stimulation used in IVF programs



gnRHa: gonadotropin releasing hormone agonist analogues; hMG: human menopausal gonadotropin; FSH: follicle stimulating hormone; hCG: human chorionic gonadotropin.
Adapted from Barbieri, RL. Assisted Reproduction. In Reproductive Endocrinology, 4th edition, Yen, SSC, Jaffe, RB, Barbieri, RL (eds), Saunders, Philadelphia, 1999, p 603.

UpToDate

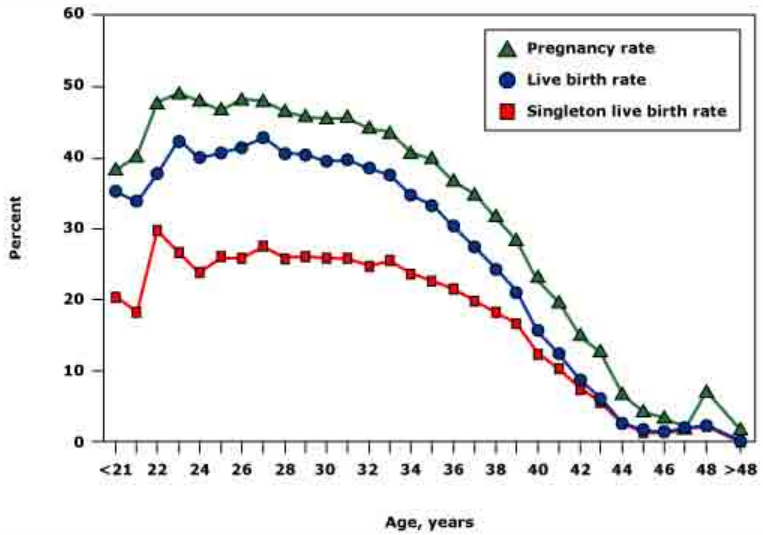
Synchronization schedule between an egg donor and female recipient



Schematic figure demonstrating a typical synchronization schedule between an egg donor and the female recipient. Cleavage stage embryos are transferred on day 3 and blastocysts on day 5 post-fertilization.

TECNICHE DI FECONDAZIONE ASSISTITA - ART

Percentages of ART cycles using fresh nondonor eggs or embryos that resulted in pregnancies, live births, and singleton live births, by age of woman,* 2006



A woman's age is the most important factor affecting the chances of a live birth when her own eggs are used. The above figure shows the percentages of pregnancies, live births, and singleton live births for women of different ages who had ART procedures using fresh nondonor eggs or embryos in 2006. The percentages of ART cycles resulting in live births and singleton live births are different because of the high percentage of multiple-infant deliveries counted among the total live births. The percentage of multiple-infant births is particularly high among women younger than 35. Among women in their 20s, the percentages of ART cycles resulting in pregnancies, live births, and singleton live births were relatively stable; however, success rates declined steadily from the mid-30s onward.

* For consistency, all percentages are based on cycles started.

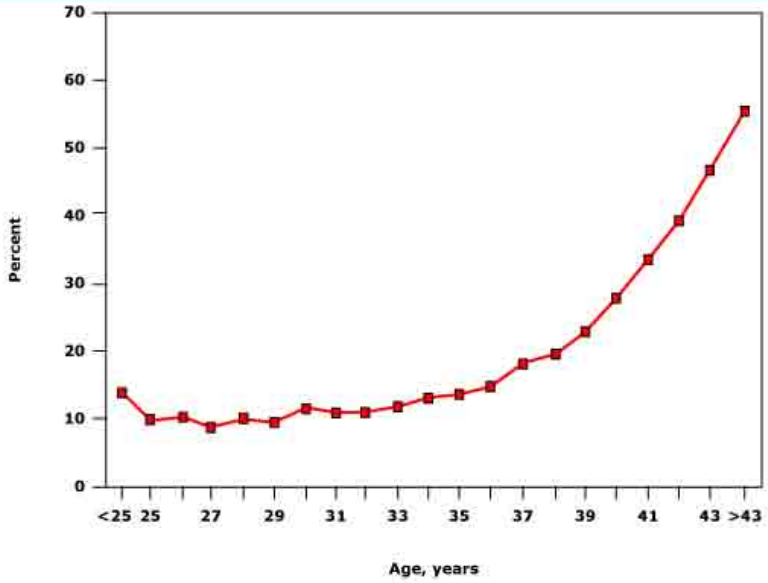
Reproduced from: Centers for Disease Control and Prevention, American Society for Reproductive Medicine, Society for Assisted Reproductive Technology. 2006 Assisted Reproductive Technology Success Rates: National Summary and Fertility Clinic Reports, Atlanta: Centers for Disease Control and Prevention, 2008.

UpToDate

TECNICHE DI FECONDAZIONE ASSISTITA - ART

Roma,
9-11 novembre 2012

Percentages of ART cycles using fresh nondonor eggs or embryos that resulted in miscarriage, by age of woman, 2006



A woman's age not only affects the chance for pregnancy when her own eggs are used, but also affects her risk for miscarriage. The above figure shows the percentages of ART cycles started in 2006 that resulted in miscarriage for women of different ages. The percentages of ART cycles that resulted in miscarriage were below 14 percent among women younger than 35. The percentages of ART cycles that resulted in miscarriages began to increase among women in their mid- to late 30s and continued to increase with age, reaching 28 percent at age 40 and 56 percent among women older than 43.

The risk for miscarriage observed among women undergoing ART procedures using fresh nondonor eggs or embryos appear to be similar to those reported in various studies of other pregnant women in the United States.

Reproduced from: Centers for Disease Control and Prevention, American Society for Reproductive Medicine, Society for Assisted Reproductive Technology. 2006 Assisted Reproductive Technology Success Rates: National Summary and Fertility Clinic Reports, Atlanta: Centers for Disease Control and Prevention, 2008.

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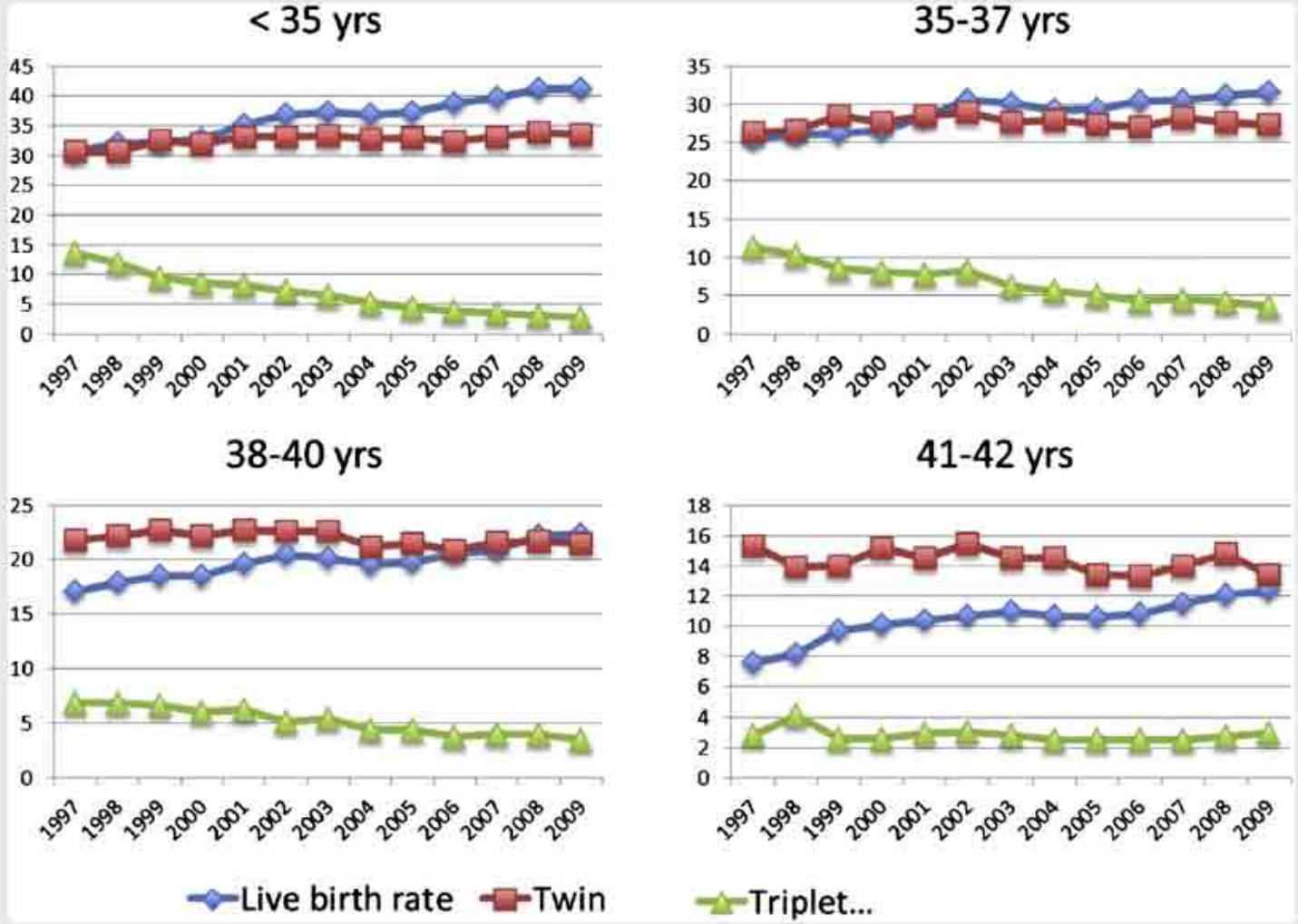
FIGURE 1



Rates of live birth, twin pregnancy, and high-order multiple pregnancy in women undergoing IVF, 1997–2009, according to the US Centers for Disease Control and Prevention National Summary and Fertility Clinic Report (39).

Beall. History of ovarian stimulation. Fertil Steril 2012.

Estimated pregnancy rate and cost per cycle for treatment of unexplained infertility

Intervention	Pregnancy rate per cycle, percent	Cost per cycle in US dollars
Expectant management	1 to 3	less than 50
IUI	4 to 6	300
Clomiphene citrate	4 to 6	100
Clomiphene plus IUI	7 to 9	400
Gonadotropin injection	4 to 10	2,000
Gonadotropin injection plus IUI	9 to 16	2,300
In vitro fertilization	20 to 40	12,000

IUI: Intrauterine insemination.

GRAZIE PER L'ATTENZIONE