

Infertility

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Infertility

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Definitions

- **Infertility** : absence of conception after 12 months of regular, unprotected intercourse (commonly used medical definition of infertility). Inability to conceive within two years of exposure to pregnancy is the epidemiological definition recommended by the World Health Organization.
- **Primary infertility** means that the couple has never conceived, despite regular unprotected intercourse for a period of 12 months.
- **Secondary infertility** means that the couple has previously conceived, but is subsequently unable to conceive despite regular unprotected intercourse for a period of 12 months. If the woman has breastfed a previous infant, then exposure to pregnancy is calculated from the end of lactational amenorrhea.
- **Childlessness (demographic studies)** : inability to bear any children, either due to the inability to conceive or the inability to carry a pregnancy to a live birth. Childlessness at the end of the reproductive years is most effectively studied by using women in the oldest age cohort: women 45 to 49 years.
- **Infertility (demographic studies)** : inability of a non-contracepting sexually active woman to have a livebirth. Demographers have shifted the endpoint from conceptions to live births because it is difficult to collect complete data about conceptions in population-based studies. In addition, demographic analyses of infertility are often based on secondary data from demographic surveys that contain complete birth histories, but no information about induced abortions, miscarriages and stillbirths. It is common in demographic studies to use a period of exposure of five years.
- **Fecundability** : the probability of conception per menstrual cycle or monthly probability of conception for a sexually active couple not using birth control.

Influence of maternal and paternal age on fecundability

The observed proportion of planned pregnancies leading to birth conceived in ≤ 6 or in ≥ 12 months according to the father's and the mother's age

		Percentage of couples conceiving within specified time interval (months)	
Age groups	No. of couples	6	12
Father's age (years)			
≤ 24	643	77.1	91.9
25-29	2692	78.4	91.3
30-34	2809	73.8	87.5
35-39	1153	68.6	83.3
≥ 40	573	66.3	81.3
Total n	7870		
Mother's age (years)			
≤ 24	1625	76.4	90.2
25-29	3663	75.9	90.0
30-34	2466	73.8	86.5
35-39	680	62.8	80.6
≥ 40	81	59.3	75.3
Total n	8515		

[Ford WC, North K, Taylor H, Farrow A, Hull MG, Golding J. Increasing paternal age is associated with delayed conception in a large population of fertile couples: evidence for declining fecundity in older men. The ALSPAC Study Team \(Avon Longitudinal Study of Pregnancy and Childhood\). Hum Reprod. 2000 Aug;15\(8\):1703-8.](#)

Declining female fertility with age

- Reduced quality of oocytes
- Ovulatory disorders
- Longer exposure to the risk of genital infections and iatrogenic infertility causes
- Increased uterine pathology
- Decreased frequency of intercourse
- Decreased partner's fertility

Prevalence of infertility (subfertility)

Category of subfertility	Prevalence rates
Unresolved primary subfertility in those women having or attempting to have at least one child	2.4-5.9
Resolved primary subfertility in those women having or attempting to have at least one child	10.0-12.1
Unresolved secondary subfertility in those women having or attempting to have more than one child	4.2-7.2
Resolved secondary subfertility in those women having or attempting to have more than one child	12.4
Any episode of primary subfertility in those women having or attempting to have at least one child	13.3
Any episode of secondary subfertility in those women having or attempting to have more than one child	17.4
Any episode of subfertility in those women having or attempting to have at least one child	20.7-32.6

Subfertility defined as failure to conceive after 12 months of regular unprotected intercourse or the occurrence of >2 consecutive miscarriages or stillbirths.

[Greenhall E, Vessey M. The prevalence of subfertility: a review of the current confusion and a report of two new studies. Fertil Steril. 1990 Dec;54\(6\):978-83.](#)

Infecundity, Infertility, and Childlessness in Developing Countries

Definitions

- **Childlessness:** Percentage of women who are currently married, have been so for at least five years, and who have no living children.
- **Primary infertility:** Percentage of women who have been married for the past five years, who have ever had sexual intercourse, who have not used contraception during the past five years, and who have not had any births.
- **Secondary infertility:** Percentage of women with no births in the past five years but who have had a birth at some time, among women who have been married for the past five years and did not use contraception during that period.
- **Secondary infecundity:** Percentage of women with no births and no pregnancies in the past five years but who have had a birth or pregnancy at some time, among women who have been married for the past five years but did not use contraception during that period.

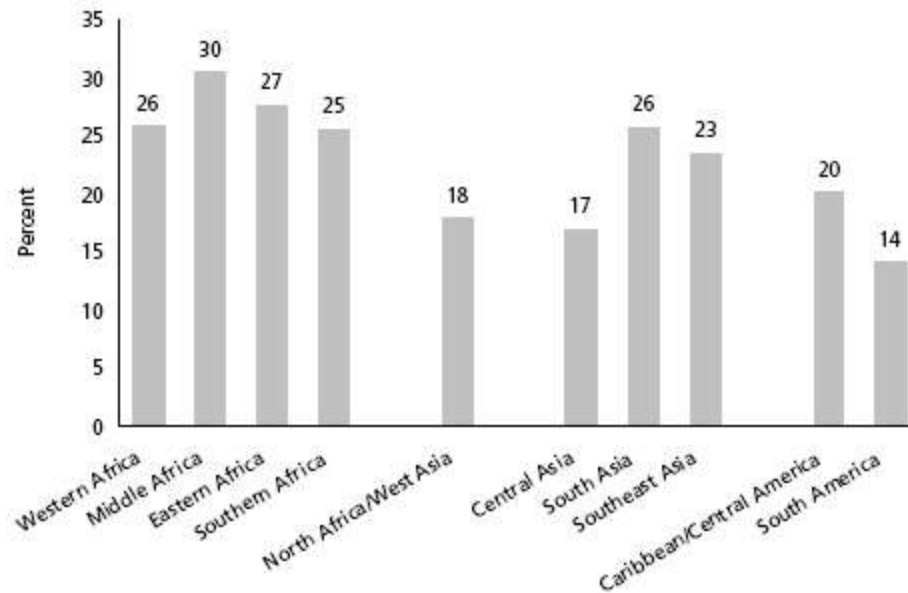
This study utilizes data from 47 Demographic and Health Surveys in developing countries to examine levels, trends, and differentials in women's inability to bear children. Overall, by age 45 to 49, only 3 percent of sexually experienced women have not had a birth. Countries with more than 5 percent of sexually experienced women age 45 to 49 without a birth include the Central African Republic, Cameroon, Mozambique, Niger, Haiti, Colombia, and Brazil.

[Rutstein, Shea O. and Iqbal H. Shah. 2004. Infecundity, Infertility, and Childlessness in Developing Countries. DHS Comparative Reports No. 9. Calverton, Maryland, USA: ORC Macro and the World Health Organization. Available from: http://www.measuredhs.com/pubs/pdf/CR9/CR9.pdf](http://www.measuredhs.com/pubs/pdf/CR9/CR9.pdf)

Infecundity, Infertility, and Childlessness in Developing Countries

Middle and Eastern Africa have the highest average levels of secondary infecundity. These subregions are followed by Western Africa, Southern Africa, and South Asia, which have similar levels. The lowest levels of secondary infecundity are in South America.

Figure 2
Percentage of women age 25-49 with secondary infecundity, by region, DHS surveys 1994-2000



Declining estimates of infertility in the United States: 1982-2002

OBJECTIVE: To determine if the decline in infertility has been uniform across subgroups.

DESIGN: Periodic data from the National Fertility Survey and the National Survey of Family Growth were used to determine which factors contributed to the decline in 12-month infertility in the United States. A woman is classified as “infertile” if she has not conceived a pregnancy after ≥ 12 months of unprotected intercourse with her husband or cohabiting partner.

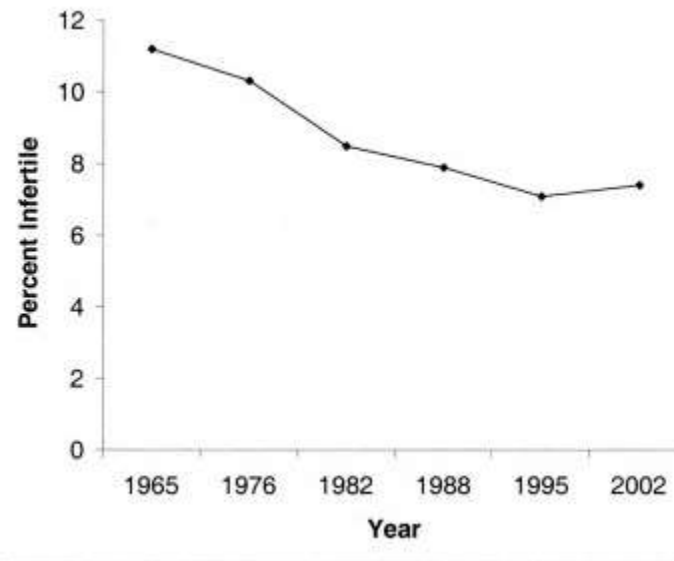
SETTING: National Survey of Family Growth, a periodic US nationally representative study.

PATIENT(S): A nationally representative sample of married women aged 15-44 years, N = 15,303 for pooled data across 4 survey years.

MAIN OUTCOME MEASURE(S): Estimates of infertility prevalence among married women aged 15-44 years.

RESULT(S): The decline in 12-month infertility in the United States from 8.5% in 1982 and 7.4% in 2002 was significant. This decline was evident in nearly all subgroups of married women. In the multivariate analysis, 12-month infertility was more likely among women who were older and nulliparous, were non-Hispanic black or Hispanic, and did not have a college degree. The decline in 12-month infertility was observed even after controlling for the compositional differences of the population over time.

CONCLUSION(S): Among married women in the United States, there has been a significant decline in 12-month infertility, which cannot be explained by changes in the composition of the population from 1982-2002.



Trends in 12-month infertility among married women aged 15–44 years, 1965–2002.

General categories of infertility, by developing status and region (WHO study)

Categories	Developed countries	Africa	Asia	Latin America	East Mediterranean
Became pregnant	12	15	16	13	15
No cause found in both	14	5	13	10	3
Female cause only	31	37	34	25	25
Male cause only	22	8	13	22	19
Causes found in both	21	35	24	30	38

Cates W, Farley TMM, Rowe PJ. Patterns of infertility in the developed and developing worlds. In: Rowe PJ, Vikhlyeva EM, editors. Diagnosis and treatment of infertility. Toronto: Hans Huber Publishers; 1988. p. 57-67.

Distribution of infertility causes in developed countries

Infertility cause	WHO 1988	France 1989	Geneva 1991
Female cause only	35%	33%	50%
Male cause only	25%	20%	27%
Cause found in both	24%	39%	20%
No cause found in both	16%	8%	3%

Specific diagnoses of infertility, by developing status and region (WHO study)

Categories	Developed	Africa	Asia	Latin America	East Mediterranean
Female diagnosis					
No demonstrable cause	40	16	31	35	26
Bilateral tubal occlusion	11	49	14	15	20
Pelvic adhesions	13	24	13	17	13
Acquired tubal abnormality	12	12	12	12	9
Anovulatory regular cycles	10	14	9	9	15
Anovulatory oligomenorrhea	9	3	7	9	11
Ovulatory oligomenorrhea	7	4	11	5	8
Hyperprolactinemia	7	5	7	8	6
Endometriosis	6	1	10	3	1
Male diagnosis					
No demonstrable cause	49	46	58	41	28

Cates W, Farley TMM, Rowe PJ. Patterns of infertility in the developed and developing worlds. In: Rowe PJ, Vikhlyaeva EM, editors. Diagnosis and treatment of infertility. Toronto: Hans Huber Publishers; 1988. p. 57-67.

Infertility treatments and subsequent pregnancies (N=444)

Treatment		Pregnancies	
		No.	%
Spontaneous pregnancies		99	22.3
Hormone treatment	<i>Female</i>	56	12.6
	<i>Male</i>	5	1.1
Antibiotic treatment of the couple		42	9.5
Surgical treatment	<i>Female</i>	38	8.6
	<i>Male</i>	2	0.5
Artificial insemination with husband semen		58	13.1
Artificial insemination with donor semen		56	12.6
IVF or ICSI		80	18.0
Pregnancies after IVF or AIH failure		8	1.8

Advice and information for the infertile couple

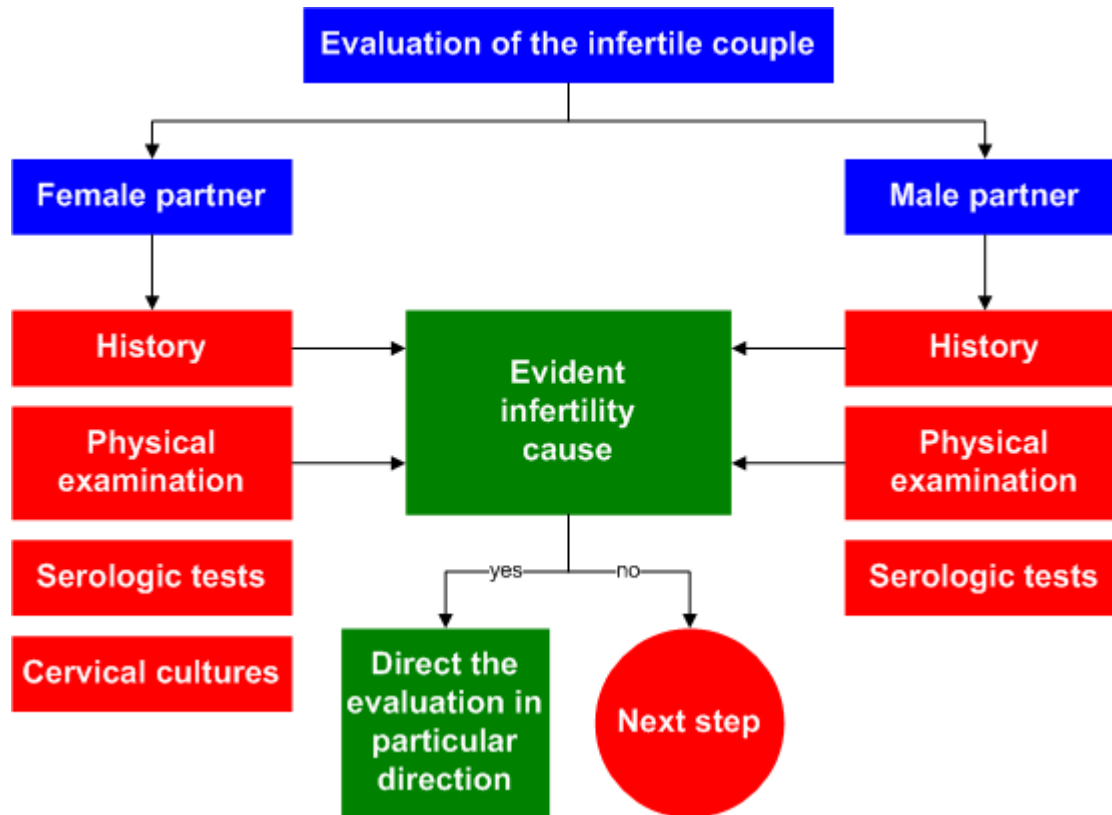
- **Information about the chances of conceiving spontaneously** may be of great help to the couple. For couples who have been trying for less than a year, the success rate is between 80% and 90%. For couples who have been trying to conceive for up to 3 years, the success rate is about 40% in a 1-year period (equivalent to a monthly fecundity rate of 4-5%). For couples who have been trying for more than 3 years, the success rate is still up to 25% in a 1-year period. If a male or female subfertility factor has been identified, there is still a likelihood of spontaneous conception, although the success rates may be lower [NHS CRD, 1992; Himmel et al, 1997; Hargreave and Mills, 1998; Te Velde and Cohlen, 1999].
- **Assessment and investigations for infertility are not generally advised until the couple has been unable to achieve a pregnancy after a year of unprotected intercourse.** Some people who present with concerns about their fertility need only simple reassurance that the chance of conception is 84% in the first year if they do not use contraception and have regular sexual intercourse. About half of couples who do not conceive in the first year will conceive in the second year (a cumulative pregnancy rate of 92%) [National Collaborating Centre for Women's and Children's Health, 2004].
- **Regular sexual intercourse (two or three times a week) throughout the cycle** should ensure that intercourse falls within the fertile period. Timing of intercourse using temperature charts and luteinizing hormone detection methods causes stress and has not been shown to improve conception rates. They are therefore not recommended [Hargreave and Mills, 1998; National Collaborating Centre for Women's and Children's Health, 2004]. [Timing intercourse to conceive](#).
- **Folic acid supplements** should be taken whilst trying to conceive and for the first 12 weeks of pregnancy in order to reduce the risk of neural tube defects. Most women should take 400 micrograms daily. A higher dose of 5 mg daily is recommended for women who either have a family history of neural tube defect, who have had a baby with a neural tube defect, who are taking antiepileptic medication, or who have coeliac disease [Wald, 1991; Lumley et al, 2003; National Collaborating Centre for Women's and Children's Health, 2004].
- **Rubella** status should be checked. If seronegative, rubella vaccination is indicated and the woman should be advised not to become pregnant within 1 month of the vaccination [CMO, 2003].

Advice and information for the infertile couple

- **Smoking cessation is advisable for both men and women.** Smoking, including passive smoking has been shown to be detrimental to fertility in women [Hughes and Brennan, 1996; Augood et al, 1998; Hull et al, 2000; BMA, 2004]. In men, although there is no clear evidence that smoking delays conception or affects fertility, it may affect sperm quality and general health [BMA, 2004].
- **Alcohol limitation**
 - Women should be advised to limit alcohol to 1 to 2 units once or twice a week. The evidence for a link between alcohol and female infertility is conflicting, and the limits for safe consumption are not known, but until more is known, low consumption of alcohol when trying to become pregnant and during pregnancy is advisable [DH, 2003; National Collaborating Centre for Women's and Children's Health, 2004]. A unit of alcohol is about the same as a small glass (125 ml) of wine or a half-pint of beer.
 - Men should be informed that alcohol consumption within the Department of Health's recommendations of 3 to 4 units a day is unlikely to affect their fertility. Excessive alcohol consumption can be detrimental to semen quality [National Collaborating Centre for Women's and Children's Health, 2004].
- **Weight**
 - Weight loss should be encouraged in women with a body mass index (BMI) greater than 29, as this is likely to increase their chance of ovulation and therefore conception. There is no proven association between male obesity and infertility, although obesity is associated with poorer general health, a reduction in sperm motility and increased DNA fragmentation [Rich-Edwards et al, 2002; Kort et al, 2003a; Kort et al, 2003b; National Collaborating Centre for Women's and Children's Health, 2004].
 - Women who have a body mass index of less than 19 and either amenorrhoea or irregular menstruation should be advised that gaining weight is likely to increase their chance of conception [National Collaborating Centre for Women's and Children's Health, 2004].
- **Nutrition**
 - A well-balanced diet will contribute to general good health for both partners. Although there is little research on nutritional factors in infertility, there have been studies suggesting that nutritional deficiencies may play a role; e.g. vitamins C, D, E, selenium, zinc, and folate deficiencies may affect sperm quality [Wong et al, 2000].
 - There is no consistent evidence to link consumption of caffeinated beverages (tea, coffee, and cola) and infertility [National Collaborating Centre for Women's and Children's Health, 2004].
- **Clothing.** Men should be informed that although there is an association between an elevated scrotal temperature and reduced semen quality, it is uncertain whether wearing loose-fitting underwear improves semen quality [Tiemessen et al, 1996; Munkelwitz and Gilbert, 1998; National Collaborating Centre for Women's and Children's Health, 2004].

Management of the infertile couple

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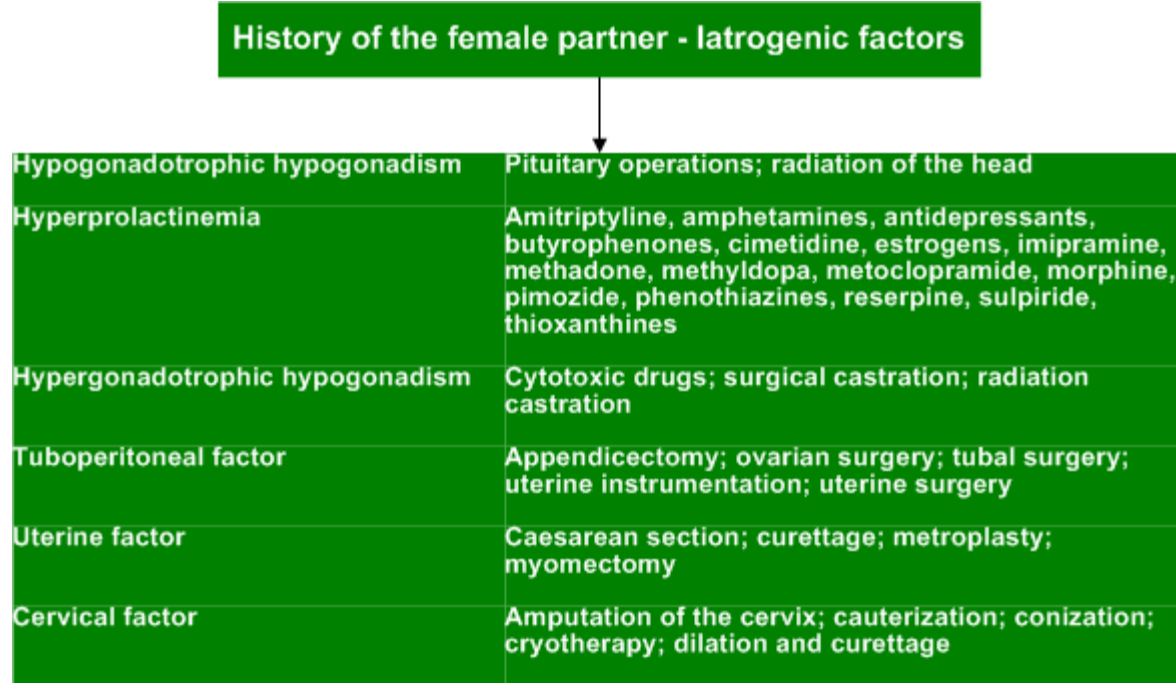
History of the female partner

Iatrogenic factors

General data, fertility history	Age; ethnic group; religion; occupation; duration of infertility; number and outcome of previous pregnancies; postpartum or abortion complications
Family history	Infertility; spontaneous abortion; stillbirths; genetic diseases; DES exposure in utero
General history	Diabetes; thyroid disease; adrenal disease; tuberculosis; autoimmune disease; other systemic diseases; iatrogenic factors
Gynecological history	Previous use of contraceptive methods; PID; STD; recurrent vaginitis, cervicitis or cystitis; iatrogenic factors
Menstrual history	Age at menarche; menstrual rhythm; duration and amount of bleeding; dysmenorrhea; premenstrual syndrome; abnormal bleeding
Symptoms and signs related to ovulatory disorders	Stress, psychologic factors; anorexia, weight loss, exercise; bulimia; overweight, obesity; anosmia; galactorrhea; hirsutism; hot flushes; cyclic pelvic pains
Habits	Occupational or environmental exposures; nutritional habits; sport; smoking; alcohol; drug consumption
Sexual history	Knowledge and use of the fertile period; frequency of vaginal intercourse; dyspareunia; orgasm

Management of the infertile couple

History of the female partner - Iatrogenic factors



Hypogonadotropic hypogonadism	Pituitary operations; radiation of the head
Hyperprolactinemia	Amitriptyline, amphetamines, antidepressants, butyrophenones, cimetidine, estrogens, imipramine, methadone, methyl dopa, metoclopramide, morphine, pimozide, phenothiazines, reserpine, sulpiride, thioxanthines
Hypergonadotropic hypogonadism	Cytotoxic drugs; surgical castration; radiation castration
Tuboperitoneal factor	Appendectomy; ovarian surgery; tubal surgery; uterine instrumentation; uterine surgery
Uterine factor	Caesarean section; curettage; metroplasty; myomectomy
Cervical factor	Amputation of the cervix; cauterization; conization; cryotherapy; dilation and curettage

Management of the infertile couple

History of the male partner

Iatrogenic factors

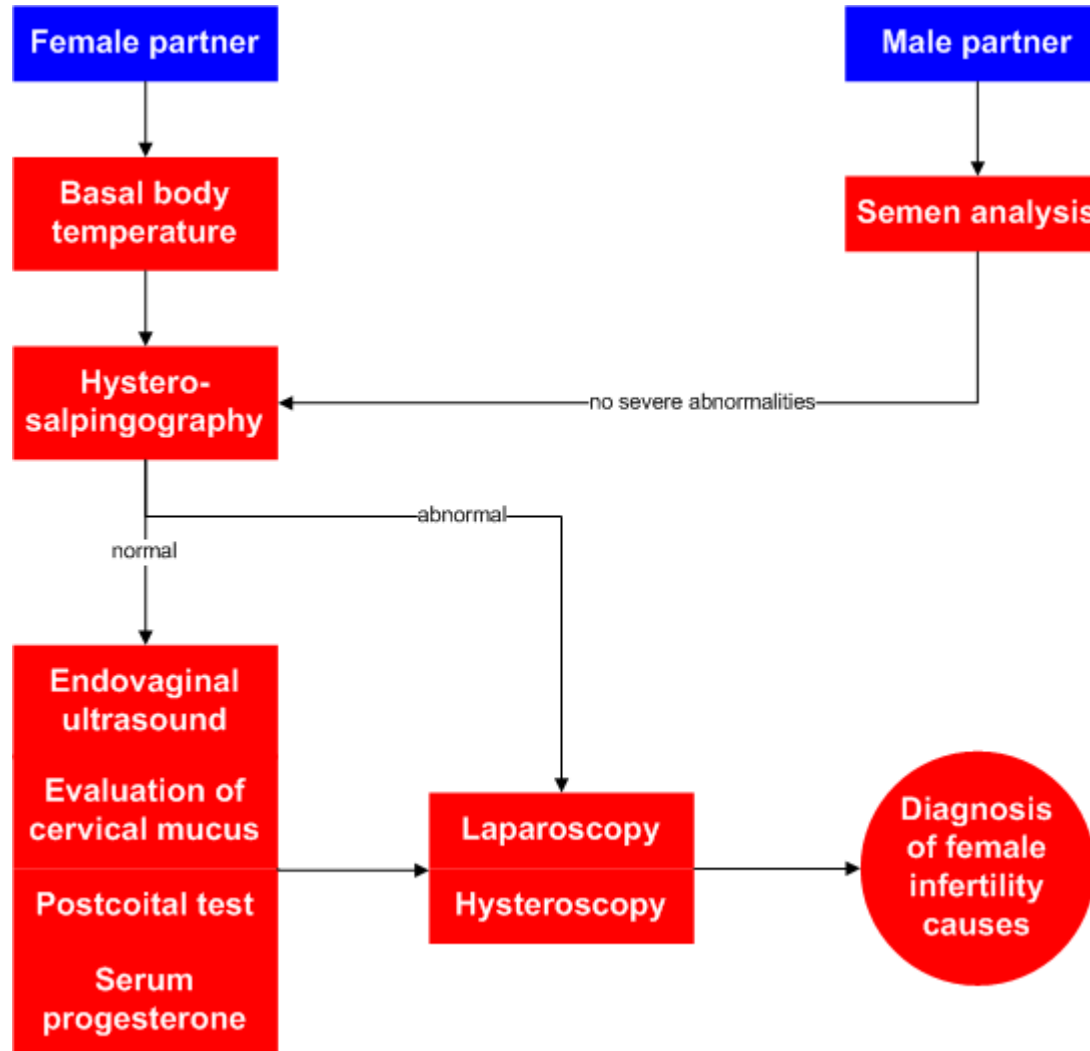
General data, fertility history	Age; ethnic group; religion; occupation; previous marriages and their outcome; primary or secondary infertility; duration of infertility
Family history	Infertility; spontaneous abortion; stillbirths; genetic diseases
General history	Diabetes; adrenal disease; cystic fibrosis; tuberculosis; bronchiectasis; chronic infections; high fever (in the past 6 months); allergies; renal diseases; liver diseases; neurological diseases; drugs
Urogenital history	Cryptorchidism; precocious or delayed puberty; testicular injury; orchitis (mumps); history of STD; epididymitis; prostatitis; vesiculitis; urethritis; genital dermatosis
Surgery relevant to infertility	Orchiopexy; orchiectomy; inguinal hernia operation; testicular detorsion; varicocelectomy; epididymovasostomy; vasovasostomy; vasectomy; prostatectomy; bladder operations; repair of hypospadias; circumcision
Habits	Occupational or environmental exposures; nutritional habits; sport; smoking; alcohol; drug consumption; sauna; tight pants
Sexual history	Knowledge and use of the fertile period; frequency of intercourse; libido; erection; dyspareunia; ejaculation; orgasm

Management of the infertile couple

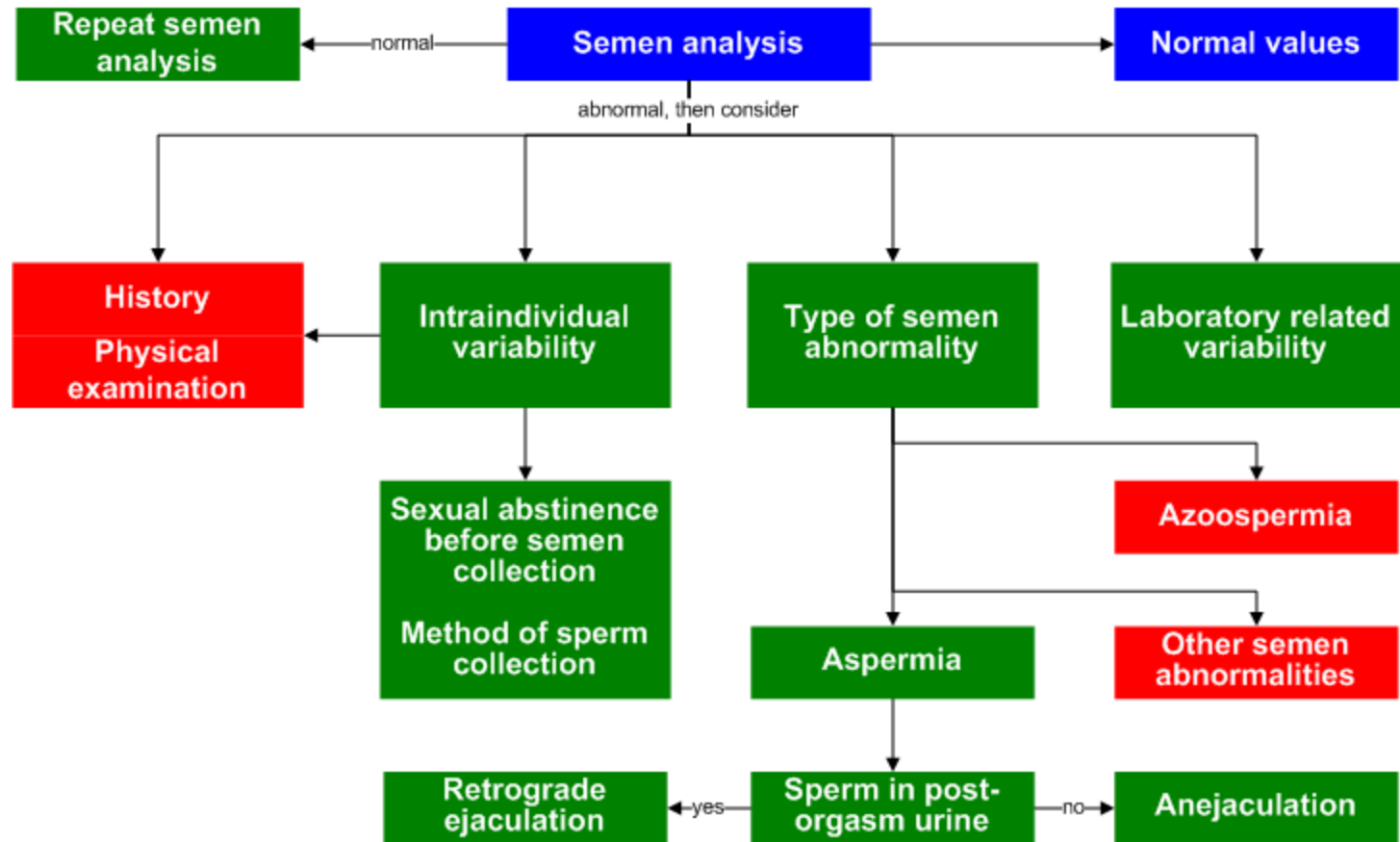
History of the male partner - Iatrogenic factors, occupational and environmental exposures

Hypogonadotropic hypogonadism	Androgens; cyproterone; medroxyprogesterone acetate; pituitary operations; radiation of the head
Hyperprolactinemia	Amitriptyline, amphetamines, antidepressants, butyrophenones, cimetidine, estrogens, imipramine, methadone, methyldopa, metoclopramide, morphine, pimozide, phenothiazines, reserpine, sulpiride, thioxanthines
Hypergonadotropic hypogonadism	Anti-infectious agents, cytotoxic drugs, heroine, spironolactone; surgical testicular injury; radiation therapy; anesthetic gases, boron, cadmium, carbon disulphide, heat, lead, mercury, pesticides, radiation
Asthenozoospermia	Atropine, antidepressants, anti-infectious agents, chlorpromazine, diazepam, local anesthetics, metoclopramide, phentolamine, propranolol; cadmium, copper, silver
Obstructive pathology	Deferential surgery; epididymal surgery; inguinal hernia repair; orchiopexy; prostatic surgery; vesical surgery; mercury

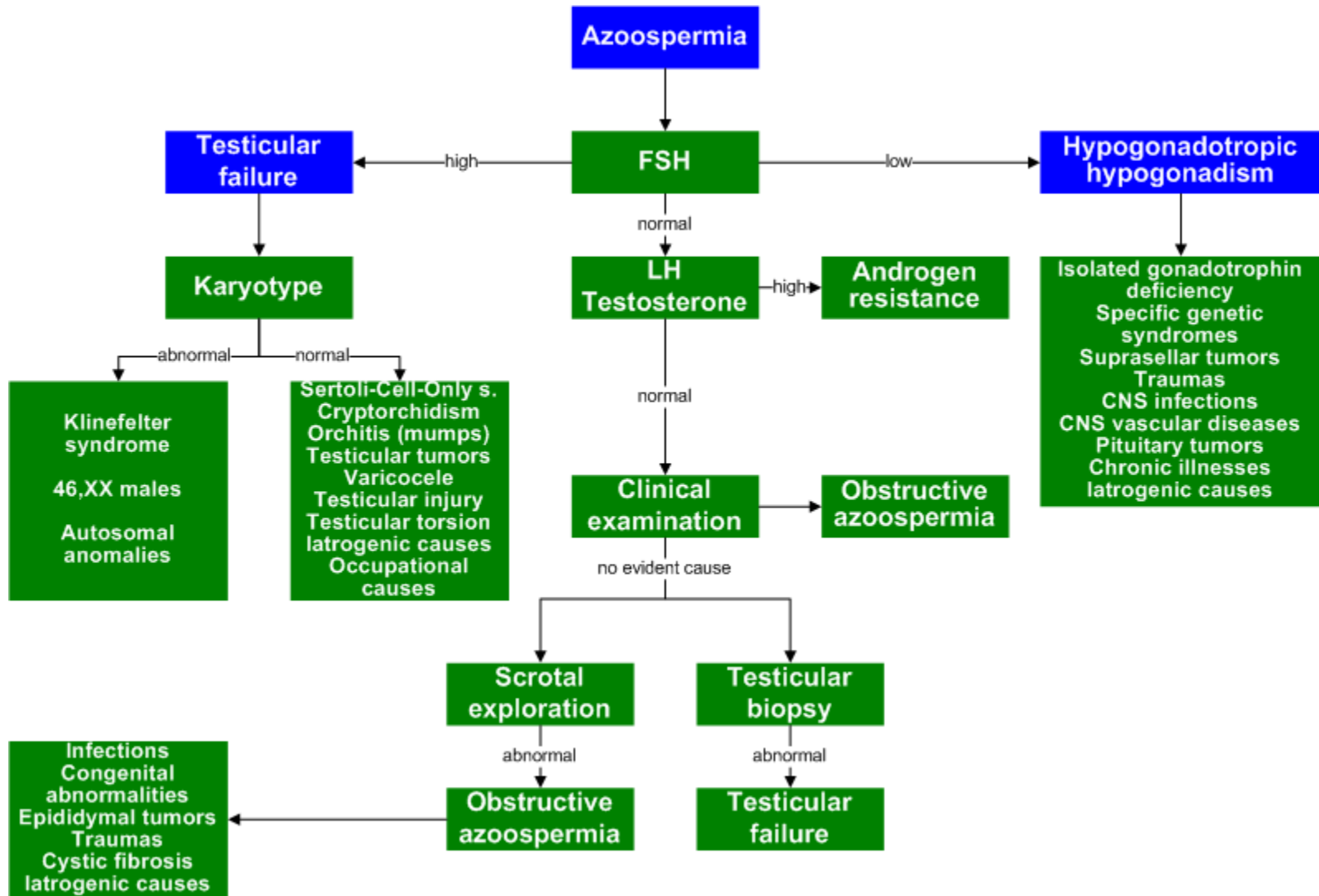
Management of the infertile couple



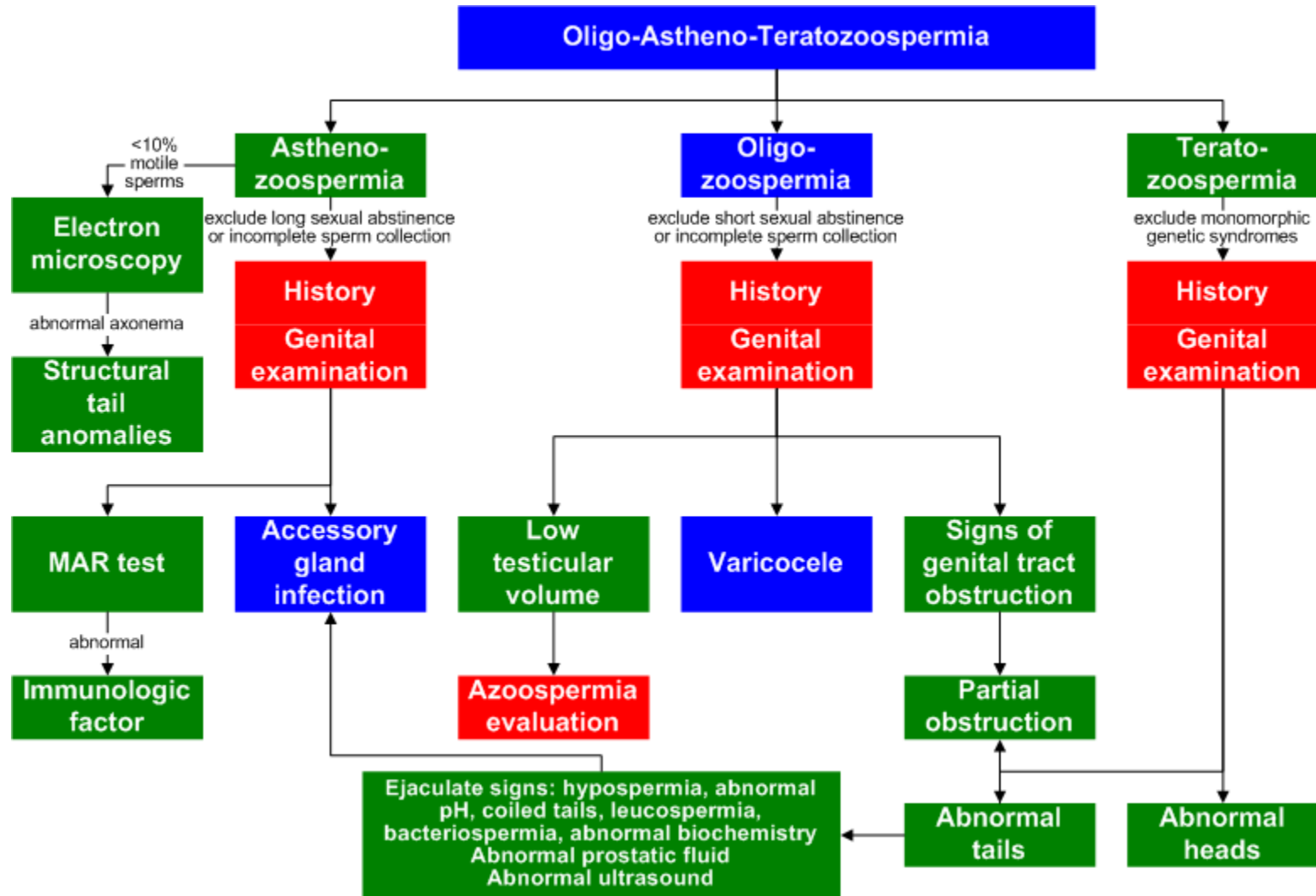
Management of the infertile couple



Management of the infertile couple



Management of the infertile couple



Evidence-based recommendations

Investigation of fertility problems and management strategies

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

Medical and surgical management of male factor fertility problems

- Men with **idiopathic semen abnormalities** should **not be offered anti-oestrogens, gonadotrophins, androgens, bromocriptine or kinin-enhancing drugs** because they have not been shown to be effective.
- Men should be informed that the **significance of antisperm antibodies is unclear** and the **effectiveness** of systemic **corticosteroids** is **uncertain**.
- Men with **leukocytes** in their **semen** should **not** be offered **antibiotic treatment unless there is an identified infection** because there is no evidence that this improves pregnancy rates.
- Men should **not be offered surgery for varicoceles** as a form of fertility treatment because it does not improve pregnancy rates.

Ovulation induction

• **Polycystic ovary syndrome**

- Women with World Health Organization Group II ovulation disorders (hypothalamic pituitary dysfunction) such as polycystic ovary syndrome should be offered treatment with **clomifene citrate** (or tamoxifen) as the **first line of treatment for up to 12 months** because it is likely to induce ovulation.
- Anovulatory women with **polycystic ovary syndrome who have not responded to clomifene citrate and who have a body mass index of more than 25** should be offered **metformin combined with clomifene citrate** because this increases ovulation and pregnancy rates.
- Women with **polycystic ovary syndrome who have not responded to clomifene citrate** should be offered **laparoscopic ovarian drilling** because it is as effective as gonadotrophin treatment and is not associated with an increased risk of multiple pregnancy.
- Women with World Health Organization Group II ovulation disorders such as **polycystic ovary syndrome who do not ovulate with clomifene citrate** (or tamoxifen) **can be offered treatment with gonadotrophins**. Human menopausal gonadotrophin, urinary follicle-stimulating hormone and recombinant follicle-stimulating hormone are equally effective in achieving pregnancy and consideration should be given to minimising cost when prescribing.
- Women with World Health Organization Group II ovulation disorders such as **polycystic ovary syndrome who ovulate with clomifene citrate but have not become pregnant after 6 months** of treatment should be offered **clomifene citrate-stimulated intra-uterine insemination**.
- The **effectiveness of pulsatile gonadotrophin-releasing hormone in women with clomifene citrate-resistant polycystic ovary syndrome is uncertain** and is therefore not recommended outside a research context.

• **Hyperprolactinaemia**

- Women with ovulatory disorders due to **hyperprolactinaemia** should be offered treatment with **dopamine agonists** such as bromocriptine. Consideration should be given to safety for use in pregnancy and minimising cost when prescribing.

Unexplained infertility

- Women with **unexplained fertility problems** should be informed that **clomifene citrate** treatment **increases the chance of pregnancy**, but that this needs to be balanced by the possible risks of treatment, especially multiple pregnancy.