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Investigating a Subfertile Couple

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Subfertility or infertility is defined by the World Health Organization (WHO) as failure to conceive over 12 months of unprotected frequent intercourse. This definition was based on an observation made by Tietze et al[1] in 1950, who reported that 90% of 1,700 couples conceived after 1 year. Such a definition serves as a good practical guide to identify those couples who deserve further evaluation for the causes of subfertility. However, there are many exceptions to this rule. If the history is suggestive of a cause for subfertility, the couple should be subject to evaluation early. Subfertility affects 10 to 15% of couples worldwide.[2-4] This figure may rise in the near future as increasing numbers of women delay childbearing to the last two decades of their reproductive life when natural fertility is in decline, resulting in increased aneuploidy of oocytes[5] and increased incidence of endometriosis and uterine pathology such as leiomyoma and adenomyosis.

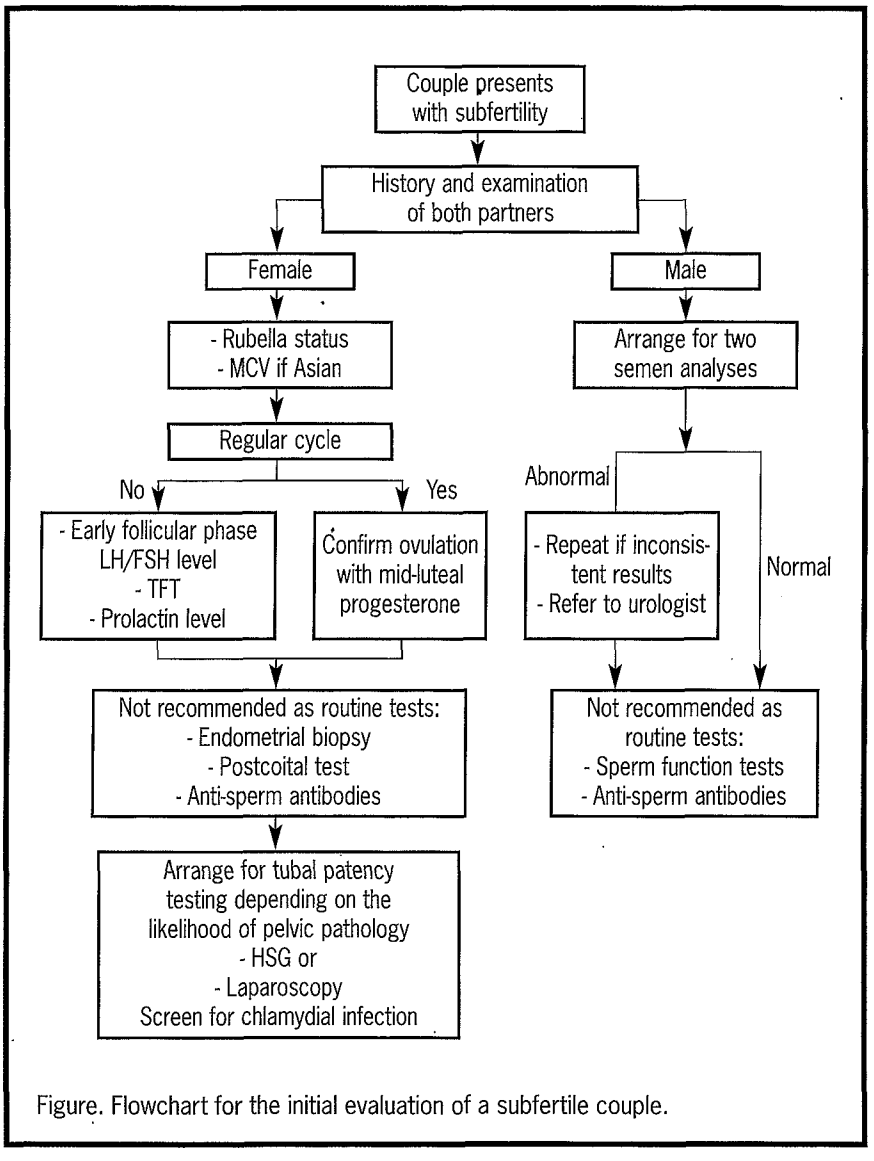

Figure. Flowchart for the initial evaluation of a subfertile couple.

Table 1. History & Examination of a Subfertile Couple

	Female	Male
History	- Ovulatory cause: cycle duration, headaches, visual disturbances, galactorrhoea if oligomenorrhoeic - Endometriosis: dysmenorrhoea, dyspareunia - Tuboperitoneal cause: history of pelvic inflammatory disease, sexually transmitted disease, or pelvic surgery - Previous pregnancies and contraception	- Testicular descent - Genital tract infection, surgery or trauma - Drug use - Chronic illness - Occupational exposure to heat - Previous pregnancies
Examination	- Secondary sexual characteristics - Thyroid - Breasts - Abdominal and pelvic findings suggestive of endometriosis or pelvic inflammatory disease	- Secondary sexual characteristics - Examination of the testes, especially the site and size; determine the testicular size with a Prader orchidometer - Epididymal swelling - Presence of vas deferens - Clinical varicocele
Details of Intercourse	- Frequency - Any erectile problem - Ejaculatory function	

Initial evaluation of a subfertile couple serves to determine the aetiology(ies) of subfertility, and to screen for those who need further and more specific assessment. It also helps to guide treatment options, and to predict success, both with and without treatment. An overview of the algorithm for evaluating a subfertile couple is shown in the Figure.

CAUSES OF SUBFERTILITY

The incidence of aetiological factors in subfertility varies in different geographical areas. Data derived from tertiary referral centres are biased. Nevertheless, these data allow investigations to be directed towards identification of these disorders. Causes of subfertility include male factors, ovulatory dysfunction, pelvic endometriosis, and tuboperitoneal factors. It is common to find a combination of factors in some couples. In about 10 to 15% of subfertile couples, no cause can be found.[6]

INITIAL CONSULTATION

It is extremely important to regard the couple as a unit and to evaluate them in a parallel manner. Male and female partners must be counselled and included in therapeutic decision-making processes. Exclusion of the male partner, for example, leads to feelings of isolation in the female and disinterest and lack of cooperation in the male. However, each partner should be examined separately so that they have the opportunity to give any sensitive past history which the other partner may be unaware of. A summary of the history and examination of a subfertile couple is given in Table 1.

The initial evaluation begins with a detailed history and physical examination of each partner. Details of intercourse should be assessed, including the frequency, and ejaculatory and erectile func-

tion. Specifically, in the female, previous pregnancies, abortions, and contraception history should be documented. Her age, duration of infertility, smoking, drinking, any hirsutism, obesity and BMI should be recorded. Long menstrual cycles may denote ovulatory cause. Further enquiry about headaches, visual disturbances, and galactorrhoea may reveal hyperprolactinaemia. Patients with polycystic ovary syndrome (PCOS) should be screened for diabetes mellitus because of increased risk in these women. Gradually worsening dysmenorrhoea and dyspareunia may be symptoms of endometriosis. Pelvic adhesions and tubal damage may result from a history of pelvic inflammatory disease (PID), sexually transmitted disease or pelvic surgery, such as ovarian cystectomy. Physical examination should include assessment of secondary sexual characteristics, the thyroid, breasts and blood pressure. Abdominal and pelvic findings suggestive of endometriosis or PID should be sought.

In the male, enquiry should be made regarding testicular descent and any treatment for maldescent, genital tract infection, surgery or trauma. Drug use, especially cytotoxics or habitual drugs including nicotine, should be sought. Chronic illness, particularly renal disease – which has an ill-defined effect on spermatogenesis, should be looked for. Occupational exposure to heat, drugs, radiation and chemicals should be included, although their relevance to subfertility has always been difficult to define. Physical examination of the male partner is mandatory if the semen analysis is abnormal. This should include a general and genital tract assessment, as well as secondary sexual characteristics. Attention should be directed to signs of hypogonadism and gynaecomastia. Determination of the consistency, site and size of the testes often provides a first diagnostic clue to spermatogenesis as testis size is correlated to sperm count. Testicular size can be determined by the Prader orchidometer. Epididymal swelling and tenderness are important findings. If the testes are absent from the scrotum, and are impalpable up to the external inguinal ring, then cryptorchidism must be assumed. The presence or absence of the vas deferens should be looked for, as well as a clinical varicocele.

Table 2. Semen Analysis: Normal Values

Parameter	Normal Value
Ejaculate volume	≥ 2.0 ml
Sperm concentration	≥ 20 x 10^6 spermatozoa/ml
Total sperm count	≥ 40 x 10^6 spermatozoa per ejaculate
Motility	≥ 50% with forward progression or ≥ 25% progressive motility within 60 minutes of ejaculation
Morphology	Individualized

Source: reference 8.

INVESTIGATIONS

Evaluation of the Male Partner

Male factor is the dominant cause of subfertility in one third of couples.[7] Evaluating the semen sample of the male partner is therefore mandatory and is often the first test to be carried out because of its non-invasiveness. A carefully performed semen analysis provides important information concerning the male reproductive hormonal cycle, spermatogenesis, and the patency of the reproductive tract. The WHO laboratory manual for the examination of human semen is the most widely adopted standard for normal values and proper testing techniques.[8] The normal values are listed in Table 2. Since morphology assessment remains subjective, a normal reference value cannot be established. It is recommended that each laboratory determine its own reference range, especially with regard to morphology, by evaluating samples of men

who have recently achieved a pregnancy.

It must be noted that the WHO criteria of normality are not related to fertility, but are the range of values to be found in healthy men. A prospective study to analyze the relation between semen variables and achievement of spontaneous conception has been published.[9] Unfortunately, there was extensive overlap between fertile and subfertile men in all three measurements. Although each of the sperm measurements helped to distinguish between fertile and infertile men, none was a powerful discriminator. The subfertile ranges were a sperm concentration $<13.5 \times 10^6$ per millilitre, less than 32% of sperm with progressive motility, and less than 9% with normal morphological features. However, it must be stressed that none of these measurements are diagnostic of subfertility.

Interpretation of semen analysis must take into consideration the variations between samples that exist in individuals.[10] There is little evidence to recommend whether one semen analysis is enough for screening purposes or whether multiple samples are necessary. However, variation within individuals is sufficient to warrant multiple specimens before a diagnosis is made, especially when the first semen analysis is abnormal.

The standard technique for semen collection is equally important. The male partner should be instructed to abstain for 3 to 4 days. With each day of abstinence up to 1 week, semen volume increases by 0.4 ml, sperm concentration by 10 to 15 million/ml, and total sperm count by 50 to 90 million. Sperm motility and morphology appear to be unaffected by 5 to 7 days of abstinence, but longer periods lead to impaired motility.[11] The male partner should produce the sample by masturbation directly into a wide-mouth sterile plastic specimen pot, but not by coitus interruptus. Condoms or lubricant jellies should not be used for collection of the sample. The sample should be delivered to the laboratory as quickly as possible, and be kept from extremes of temperature during transport.

Assessment of Ovulation

The only absolute proof of ovulation is pregnancy. All other tests are inferential. These include menstrual cycle history, basal body temperature (BBT) measurement, mid-luteal serum progesterone, detection of luteinizing hormone (LH) surge, and ultrasonographic disappearance of the dominant follicle.

Women with periods that occur at 26- to 36-day intervals are likely to be ovulatory, but not invariably. It is advisable to confirm ovulation in regularly menstruating women as up to 9% of regular menstrual cycles are anovulatory.[12] The concentration of progesterone in blood begins to rise within 12 hours of the start of the LH surge. The progesterone causes a rise in BBT, which is sustained throughout the luteal phase, giving a characteristic biphasic pattern. BBT is non-invasive but tedious. It is not as accurate as mid-luteal progesterone in confirming ovulation. Monophasic BBT has been observed in ovulatory menstrual cycles.[13,14]

The often imprecise measurement of BBT has largely been replaced by the simple measurement of mid-luteal serum progesterone level, which is to be taken 7 days prior to the next menstruation, i.e. Day 21 in a woman with a regular 28-day cycle. A level greater than 30 nmol/L indicates the presence of a corpus luteum. A modestly elevated progesterone level may indicate that the sample was not taken in the mid-luteal phase and a repeat sample is warranted. Measuring mid-luteal progesterone is by far the best test for confirming ovulation, and is the test recommended by the Royal College of Obstetricians & Gynaecologists.[15]

Ovulation takes place 37 to 38 hours after the LH surge, a result of the positive feedback from increased estradiol secretion by the dominant follicle. Thus, measurements of estradiol and LH in blood have high predictive value because the magnitude of the change in concentration of the LH surge is

obvious.[16] This method requires blood-taking for a few consecutive days and is therefore impractical as a routine investigation test. Detection of LH in the urine is simple, but it gives a higher incidence of false negative results than the serum test.[17,18] A false positive result is possible in those women with PCOS whose serum LH level is constantly elevated.[19]

Direct observation of the collapse of the ovulatory follicle and the appearance of fluid in the pouch of Douglas with transvaginal ultrasound[20,21] is generally too inconvenient and labour intensive. The intensive, sequential ultrasound monitoring required to make the diagnosis can be both expensive and misleading.

Endometrial biopsy evaluates the cumulative effect of progesterone on the endometrium. The invasiveness precludes its use as a confirmatory test for ovulation. A timed endometrial biopsy has been traditionally used to diagnose luteal phase defect when endometrial biopsies in two different menstrual cycles show delayed histological maturation of more than 2 days. Not only is this test subjective to individual assessment, it does not predict pregnancy reliably.[22,23] This lack of evidence suggests that the luteal phase should not be routinely evaluated with an endometrial biopsy in all couples.

On the other hand, an irregular menstrual cycle is an indicator for further tests to find out the causes of anovulation. An elevated follicle stimulating hormone (FSH) level during the follicular phase will identify premature ovarian failure, which may present early in its course without a history of hot flushes. An elevated LH/FSH ratio and slightly elevated androgen levels may delineate the woman with PCOS. Pelvic ultrasound scanning may then show multiple small follicles of less than 10 mm on both ovaries. Serum prolactin level and thyroid function test should also be performed. A totally aberrant bleeding pattern warrants further investigations on its own, so as to rule out pathologies such as cervical or uterine polyps. For example, in patients with chronic anovulation and aberrant menstrual pattern, endometrial hyperplasia should be excluded, usually by means of endometrial biopsy.

Evaluation of Tubal Patency

Hysterosalpingogram (HSG) provides information regarding the shape of the uterine cavity and patency of the fallopian tubes. It should be performed in the early follicular phase of the cycle, as soon as menstrual bleeding has ceased. This eliminates the risk of blood reflux or having to perform the procedure during early conception. Pain and discomfort is common during the procedure, especially when there is tubal blockage. Vasovagal reaction can occur if the pain is severe. Pelvic infection developed in 0.3 to 4.0% of patients undergoing HSG.[15] It involves exposure to ionizing radiation and iodinated contrast material. The major disadvantage with HSG is the inability to diagnose peritubal adhesions.[24] It can be used as a screening test for low-risk couples. The positive predictive value for tubal patency is so low that an abnormal HSG will require further verification with laparoscopy.

Laparoscopy is the gold standard for the accurate assessment of tubal patency. It allows direct visualization of the pelvis, and hence allows the diagnosis of endometriosis or pelvic adhesions to be made. It also offers an opportunity to release the pelvic adhesions, and to restore tubal patency if there is a hydrosalpinx. There is still much debate over whether salpingostomy offers any advantage over salpingectomy on the affected Fallopian tube when there was evidence to show that salpingectomies improved *in vitro* fertilization (IVF) outcome in patients with gross bilateral hydrosalpinges visible by pelvic ultrasound scan.[25] However, it is generally agreed that attempts be made initially to restore tubal patency if the mucosa exhibits no adhesions,[26] and indiscriminate salpingectomy before IVF on women with hydrosalpinx is not advisable.[27]

Pelvic endometriotic deposits can be ablated at the time of

laparoscopy. In a randomized controlled trial, ablating minimal or mild endometriotic deposits enhances fecundity in infertile women.[28] Needless to say, any pathological ovarian cysts can be removed at the same setting and pathological diagnosis made. Therefore, those with risk factors for pelvic or tubal disease or an abnormal pelvic examination should proceed directly to laparoscopy, as they are significantly more likely to have pelvic pathology.[29] Laparoscopy involves hospital admission, general anaesthesia, a 1 to 2% complication rate (including postoperative infection and injury to bowel or blood vessels), and a mortality rate of 8 in 100,000.[30] It is also more expensive, even when done as day surgery.

Hysterosalpingo-contrast-sonography (HyCoSy) is an ultrasound-based technique that uses an echo positive fluid as a contrast agent in the evaluation of tubal patency. The aim of HyCoSy is to visualize both tubal ostia and to demonstrate the flow of ultrasound contrast medium in the Fallopian tubes. This technique is still being evaluated as a test for tubal patency.[31]

OTHER TESTS

Rubella Antibody

Although rubella is a mild infectious disease, maternal rubella infection in the first trimester of pregnancy results in severe fetal abnormalities in up to 80% of cases.[32] The risk of abnormality declines to about 25% by the end of the second trimester, and fetal damage after this stage of pregnancy is rare. Multiple defects are common, constituting the Congenital Rubella Syndrome. In order to avoid such fetal risks, all women of childbearing age should ideally know their immune status before conception so that they can be vaccinated if non-immune. When a woman presents with a subfertility problem, it offers an opportunity to check her rubella antibody status.

Mean Corpuscular Volume

Thalassaemias are the commonest genetic disorders in the world.[33] The prevalence of both α- and β-thalassaemia is higher in South East Asia. In Hong Kong, 2.2% of the population is α-thalassaemia-1 heterozygotes[34] and 6% are β-thalassaemia-1 heterozygotes.[35] Couples where both partners are α-thalassaemia-1 heterozygotes or β-thalassaemia-1 heterozygotes have a 25% risk of bearing offspring with a homozygous state of the disease. The mean corpuscular volume (MCV) of the woman can be used as a screening test. If the MCV is low, then the husband should be screened for thalassaemia with the same test. Differentiation between the two types of thalassaemia is necessary if both have low MCVs, and this can be performed by haemoglobin electrophoresis or sometimes gene mapping. At-risk couples should be counselled for prenatal diagnosis or pre-implantation genetic diagnosis, depending on the availability of these services and patients' choice.

Thyroid Function Test & Prolactin

Infertile women in general do not have more evidence of thyroid dysfunction than the general population.[36-38] Similarly, there is no association between prolactin levels and cumulative conception rates over 12 months' follow up in subfertile women with regular menstrual cycles.[39] Although there may be mild hyperprolactinaemia in regularly menstruating infertile women,[36] treatment with bromocriptine does not increase conception rates in such women when compared with placebo.[40] Therefore, thyroid function tests and prolactin estimation should be reserved for those women with amenorrhoea, oligomenorrhoea or clinical symptoms of hyperthyroidism or hyperprolactinaemia.

Chlamydia

Chlamydia trachomatis has overtaken *Neisseria gonorrhoeae* as the most common microbiological agent causing PID worldwide.[41,42] One episode of PID results in a 10% chance of tubal blockage, and the risk increases to 50% after three

episodes.[43] A meta-analysis showed that the discriminative capacity of chlamydia antibody testing for the diagnosis of any tubal pathology was equal to the discriminative capacity of HSG in the diagnosis of tubal occlusion.[44] However, it does not provide information on the uterus or tubal pathology not related to chlamydia. It remains to be proven whether chlamydia antibodies, either alone or in combination with HSG, would be a good screening test for tubal pathology as diagnosed at laparoscopy.

While the incidence of isolating *Chlamydia trachomatis* from endocervical swabs was as low as 0.01 to 1.8% in subfertile women,[45,46] it is unacceptable for their fertility to be further compromised iatrogenically during uterine instrumentation at laparoscopy or HSG. Current evidence shows that DNA amplification techniques, such as the polymerase chain reaction (PCR) or ligase chain reaction (LCR), are the most sensitive and specific methods for detecting chlamydial infection.[47,48] Conventional tests, such as cell culture and enzyme immunoassay (EIA), may grossly underestimate the prevalence of chlamydia infection. The overall sensitivity for culture was 60 to 65%, and 30 to 40% for EIA in detecting chlamydial infection detected by PCR or LCR.[49] If the DNA-based tests are not available locally, antibiotic prophylaxis should be considered instead.

Postcoital Test

The postcoital test suffers from a lack of standards with regard to normal values, methodology, and reproducibility. Even trained observers rating identical slides showed only poor to fair reproducibility with wide interobserver variation.[50] The test has poor sensitivity, specificity, and positive and negative predictive values. Hence, it lacks validity as a test for subfertility[51] and has poor prognostic value. It is only useful when underlying sexual dysfunction is suspected; then it can prove that sexual intercourse has taken place. It lacks validity as a routine investigation for subfertility.

Other Tests not Recommended as Basic Investigations for Subfertile Couples

Autoimmune anti-sperm antibodies can be found in both men and women. In men, the anti-sperm antibodies can be found on the sperm surface, in seminal plasma and/or in blood serum. In women, they can be found in blood serum or in cervical mucus. There is conflicting evidence when the association between the presence of anti-sperm antibodies and fertility is studied. They may be present in some fertile couples as well,[52] and the antibody status in either partner was not a significant independent predictor of time to pregnancy.

Specialized sperm function tests designed to detect defects in the complex processes leading to fertilization have been developed in an attempt to provide more information about male factor subfertility, and to try and refine the discrimination between those who are potentially fertile and those who are not. These include computer-assisted seminal analysis, hypo-osmotic swelling assay, sperm penetration test, hemizona assay and hamster oocyte penetration assay. None of these tests have been shown to perform well in isolation and they should be reserved as research tools rather than as routine clinical tests.

CONCLUSION

At present, agreement regarding standard basic tests for subfertile couples remains controversial. The ESHRE Capri Workshop[53] stressed that although some believe that any abnormal diagnostic test result defines a cause of subfertility, it is more probable that an abnormal test result defines a cause of infertility only when treatment of the cause enhances fecundability in comparison with no treatment. After a critical review of the literature, the group concluded that abnormal tests that have an established correlation with impaired fecundability are semen analysis, tubal patency by HSG or laparoscopy, and laboratory assessment of ovulation.

Since tubal patency may not be the only cause of subfertility, laparoscopy may also help to detect other factors, such as endometriosis and pelvic adhesions. Laparoscopy should be performed if history and examination suggest pelvic adhesions or endometriosis, or if the HSG shows abnormalities. An endocervical swab to look for *Chlamydia trachomatis* should be performed prior to these uterine instrumentation procedures. The initial consultation offers an opportunity to screen for rubella status in women, and thalassaemia in ethnic Asians. All other tests should be reserved for special indications or for academic interests.

REFERENCES

1. Tietze C, Guttmacher AF, Rusin S. Time required for conception in 1727 planned pregnancies. Fertil Steril 1950;1:338.
2. Menning BE. The psychology of infertility. In: Aimen J, ed. Infertility: Diagnosis and Management. New York: Springer-Verlag, 1984;17-29.
3. Templeton A, Fraser C, Thompson B. Infertility--epidemiology and referral practice. Hum Reprod 1991;6:1391-1394.
4. Snick HK, Snick TS, Evers JL, Collins JA. The spontaneous pregnancy prognosis in untreated subfertile couples: the Walcheren primary care study. Hum Reprod 1997;12:1582-1588.
5. Delhanty JD. Preimplantation genetics: an explanation for poor human fertility? Ann Hum Genet 2001;65:331-338.
6. Bradshaw KD, Chantilis SJ, Carr BR. Diagnostic evaluation and treatment algorithms for the infertile couple. In: Carr BR, ed. Textbook of reproductive medicine. Stamford: Appleton & Lange, 1988;549-564.
7. Jaffe SB, Jewelewicz R. The basic infertility investigation. Fertil Steril 1991;56:599-613.
8. World Health Organization. Laboratory Manual for the examination of Human Semen and Semen-Cervical Mucus Interaction, 4th edition. Cambridge: Cambridge University Press, 1999.
9. Guzick DS, Overstreet JW, Factor-Litvak P, et al. Sperm morphology, motility, and concentration in fertile and infertile men. N Engl J Med 2001;345:1388-1393.
10. Opsahl MS, Dixon NG, Robins ER, Cunningham DS. Single vs. multiple semen specimens in screening for male infertility factors. A comparison. J Reprod Med 1996;41:313-315.
11. Clark RV, Sherins RJ. Use of semen analysis in the evaluation of the infertile couple. In: Santen RJ, Swerdloff RS, eds. Male Reproductive Dysfunction. New York: Marcel Dekker, 1986;253-266.
12. Landgren BM, Unden AL, Diczfalusy E. Hormonal profile of the cycle in 68 normally menstruating women. Acta Endocrinol (Copenh) 1980;94:89-98.
13. Johansson ED, Larsson-Cohn U, Gemzell C. Monophasic basal body temperature in ovulatory menstrual cycles. Am J Obstet Gynecol 1972;113:933-937.
14. Lenton EA, Weston GA, Cooke ID. Problems in using basal body temperature recordings in an infertility clinic. Br Med J 1977;1:803-805.
15. Royal College of Obstetricians & Gynaecologists. The initial investigation and management of the infertile couple: Evidence-based clinical guidelines No. 2. London: RCOG Press, 1998.
16. O'Connor JF, Kovalevskaya G, Birken S, et al. The expression of the urinary forms of human luteinizing hormone beta fragment in various populations as assessed by a specific immunoradiometric assay. Hum Reprod 1998;13:826-835.
17. Robinson JN, Lockwood GM, Dalton JD, Franklin PA, Farr MM, Barlow DH. A randomized prospective study to assess the effect of the use of home urinary luteinizing hormone detection on the efficiency of donor insemination. Hum Reprod 1992;7:63-65.
18. Anderson RA, Eccles SM, Irvine DS. Home ovulation testing in a donor insemination service. Hum Reprod 1996;11:1674-1677.
19. Penzias AS. Current reproductive endocrinology. Obstet Gynecol Clin North Am 2000;27:473-486.
20. Collins W, Jurkovic D, Bourne T, Kurjak A, Campbell S. Ovarian morphology, endocrine function and intra-follicular blood flow during the peri-ovulatory period. Hum Reprod 1991;6:319-324.
21. Brannstrom M, Zackrisson U, Hagstrom HG, et al. Preovulatory changes of blood flow in different regions of the human follicle. Fertil Steril 1998;69:435-442.
22. Balasch J, Fabregues E, Creus M, Vanrell JA. The usefulness of endometrial biopsy for luteal phase evaluation in infertility. Hum Reprod 1992;7:973-977.
23. Giudice LC. Potential biochemical markers of uterine receptivity. Hum Reprod 1999;14(Suppl 2):3-16.
24. Swart P, Mol BW, van der Veen F, van Beurden M, Redekop WK, Bossuyt PM. The accuracy of hysterosalpingography in the diagnosis of tubal pathology: a meta-analysis. Fertil Steril 1995;64:486-491.
25. Strandell A, Lindhard A, Waldenstrom U, Thorburn J, Janson PO, Hamberger L. Hydrosalpinx and IVF outcome: a prospective, randomized multicentre trial in Scandinavia on salpingectomy prior to IVF. Hum Reprod 1999;14:2762-2769.
26. Dechaud H. Hydrosalpinx and ART: hydrosalpinges suitable for salpingectomy before IVF. Hum Reprod 2000;15:2464-2465.
27. Sharara FI. The role of hydrosalpinx in IVF: simply mechanical? Hum Reprod 1999:14:577-578.
28. Marcoux S, Maheux R, Berube S. Laparoscopic surgery in infertile women with minimal or mild endometriosis. Canadian Collaborative Group on Endometriosis. N Engl J Med 1997;337:217-222.
29. Cumming DC, Taylor PJ. Historical predictability of abnormal laparoscopic findings in the infertile woman. J Reprod Med 1979;23:295-298.
30. Chamberlain G, Brown JC. Gynaecological laparoscopy – the report of the working party of the confidential enquiry into gynaecological laparoscopy. London: RCOG Press, 1978.
31. Strandell A, Bourne T, Bergh C, Granberg S, Asztely M, Thorburn J. The assessment of endometrial pathology and tubal patency: a comparison between the use of ultrasonography and X-ray hysterosalpingography for the investigation of infertility patients. Ultrasound Obstet Gynecol 1999;14:200-204.
32. Miller E, Cradock-Watson JE, Pollock TM. Consequences of confirmed maternal rubella at successive stages of pregnancy. Lancet 1982;2:781-784.
33. Weatherall DJ. The diagnostic features of the different forms of thalassaemia. In: Weatherall DJ, ed. The Thalassaemias. Edinburgh: Churchill Livingston, 1981;1-26.
34. Chan V, Chan TK, Cheng MY, Kan YW, Todd D. Organization of the zeta-alpha genes in Chinese. Br J Haematol 1986;64:97-105.
35. Ghosh A, Woo JS, Wan CW, et al. Evaluation of a prenatal screening procedure for beta-thalassaemia carriers in a Chinese population based on the mean corpuscular volume (MCV). Prenat Diagn 1985;5:59-65.

References continued on page 32.

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establishing a cause-and-effect relationship between BV and premature labour and delivery and an effective treatment is available, we should not put forth the dictum for universal screening and treatment of BV in pregnancy to prevent premature labour and delivery. Since none of the treatment regimens have demonstrated efficacy in the treatment of BV in pregnant women, it does not seem reasonable to recommend screening and treatment for the prevention of preterm labour and delivery.

SUGGESTED READING

1. Carey JC, Klebanoff MA, Hauth JC, et al. Metronidazole to prevent preterm delivery in pregnant women with asymptomatic bacterial vaginosis. N Engl J Med. 2000;342:534-40.
2. McDonald HM, O'Laughlin JA, Vigneswaran R, et al. Impact of metronidazole therapy on preterm birth in women with bacterial vaginosis flora (Gardnerella vaginalis) a randomized placebo controlled trial. Br J Obstet Gynaecol. 1997;104:1391-1397.
3. Klebanoff MA, Carey JC, Hauth JC, et al. Failure of metronidazole to prevent preterm delivery among pregnant women with asymptomatic trichomonas vaginalis infection. N Engl J Med 2001;345:487-493.

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References to "Investigating a Subfertile Couple".

36. Laufer MR, Floor AE, Parsons KE, Kuntz KM, Barbieri RL, Friedman AJ. Evaluation of hormonal testing in the screening for in vitro fertilisation (IVF) of women with tubal factor infertility. J Assisted Reprod Genet 1995;12:93-96.
37. Shalev E, Eliyahu S, Ziv M, Ben-Ami M. Routine thyroid function tests in infertile women: are they necessary? Am J Obstet Gynecol 1994;171:1191-1192.
38. Strickland DM, Whitted WA, Wians FH Jr. Screening infertile women for subclinical hypothyroidism. Am J Obstet Gynecol 1990;163(1 pt 1):262-263.
39. Glazener CM, Kelly NJ, Hull MG. Prolactin measurement in the investigation of infertility in women with a normal menstrual cycle. Br J Obstet Gynaecol 1987;94:535-538.
40. Hughes E, Collins J, Vandekerckhove P. Bromocriptine with placebo in women with unexplained infertility. (Cochrane Review) In: The Cochrane Library, Issue 2. Oxford: Update Software; 1997.
41. Stacey CM, Munday PE, Taylor-Robinson D, et al. A longitudinal study of pelvic inflammatory disease. Br J Obstet Gynecol 1992;99:994-999.
42. Tang OS. The microbial etiology of acute pelvic inflammatory disease in Queen Mary Hospital. Hong Kong Practitioner 1996;18:92-95.
43. Westrom L, Joesoef R, Reynolds G, Hagdu A, Thompson SE. Pelvic inflammatory disease and fertility. A cohort study of 1844 women with laparoscopically verified disease and 657 control women with normal laparoscopic results. Sex Transm Dis 1992;19:185-192.
44. Mol BW, Dijkman B, Wertheim P, Lijmer J, van der Veen F, Bossuyt PM. The accuracy of serum chlamydial antibodies in the diagnosis of tubal pathology: a meta-analysis. Fertil Steril 1997;67:1031-1037.
45. Eggert-Kruse W, Rohr G, Demirakca T, et al. Chlamydial serology in 1303 asymptomatic subfertile couples. Hum Reprod 1997;12:1464-1475.
46. Ng EH, Tang OS, Ho PC. Measurement of serum CA-125 concentrations does not improve the value of Chlamydia trachomatis antibody in predicting tubal pathology at laparoscopy. Hum Reprod 2001;16:775-779.
47. Ridgway GL, Mumtaz G, Robinson AJ, et al. Comparison of the ligase chain reaction with cell culture for the diagnosis of Chlamydia trachomatis infection in women. J Clin Path 1996;49:116-119.
48. Skulnick M, Chua R, Simor AE, et al. Use of the polymerase chain reaction for the detection of Chlamydia trachomatis from endocervical and urine specimens in an asymptomatic low-prevalence population of women. Diagn Microbiol Infect Dis 1994;20:195-201.
49. Lee HH. The use of amplified nucleic acid technologies for the detection of Chlamydia trachomatis infection. In: Templeton AA, ed. The Prevention of Pelvic Infection. London: PCOG Press, 1996.
50. Glatstein IZ, Best CL, Palumbo A, Sleeper LA, Friedman AJ, Hornstein MD. The reproducibility of the postcoital test: a prospective study. Obstet Gynecol 1995;85:396-400.
51. Griffith CS, Grimes DA. The validity of the postcoital test. Am J Obstet Gynecol 1990;162:615-620.
52. Collins JA, Burrows EA, Yeo J, YoungLai EV. Frequency and predictive value of antisperm antibodies among infertile couples. Hum Reprod 1993;8:592-598.
53. ESHRE Capri Workshop. Guidelines to the prevalence, diagnosis, treatment and management of infertility, 1996. Hum Reprod 1996;11:1779-1807.