INDUCTION OF FERTILITY IN DISORDERS OF OVULATION

Pages with reference to book, From 20 To 23

Muhammad Aslam, Muhammad Amjad Hameed (Department of Physiology, Army Medical College, Rawalpindi.)
Khalida.A.K. Akhtar (Department of Obstetrics and Gynaecology, Rawalpindi Medical College, Rawalpindi.)

The fertility of a population or an individual is expressed as the number of children born. There is an urgent need of curtailing our population growth rate but the plight of issueless couples cannot as well be overlooked. Measure to induce fertility have always interested scientists, demographers, gynaecologists, general practitioners, population planners, couples and individuals. To understand various measures for the induction of fertility, it seems appropriate to look into the aetiology and the effects of disorders of ovulation to under stand the logic in therapeutics in these conditions. Causes of disorders of ovulation include hyperprolactinaemia, primary hypothalamic failure, hypothalamo-pituitary failure and defects of follicle maturation.

1. Hyperprolactinaemia

Serum prolactin level increases during pregnancy and its concentration in the third trimester rises about twentyfold than in the normal non-pregnant women[1]. The elevated prolactin concentration decreases after delivery, but episodically increases after suckling. Exercise, various forms of stress and sexual intercourse are also associated with an increase in serum prolactin level[2]. Other pharmacological and physiological stimuli including phenothiazine, haloperidol, insulin-induced hypoglycaemia, thyrotrophin-releasing hormone, oestrogens and arginine also promote prolactin secretion[3]. Abnormal prolactin secretion has been reported in a variety of endocrine, neoplastic and neurological disorders[4]. Rise in serum prolactin concentration can also occur in certain metabolic disorders, systemic illnesses or with drug ingestion. Hyperprolactinaemia, in turn, may lead to subfertility by suppressing expulsion of ovum during the mid cycle. Diagnosis is established by two or more blood samples for prolactin levels ideally collected at the same time on different days under non-stressful conditions and by x-ray tomography for the evidence of changes in the sella turcica caused by pituitary tumours which account for 25-30% of cases. Treatment is directed to the cause of hyperprolactinaemia, whenever possible. Oestrogen treatment which might seem an obvious form of therapy, only succeeds in elevating prolactin levels. Bromocriptine, an ergot derivative, is used to inhibit prolactin secretion in hyperprolactinaemia. It is now frequently used to induce fertility in such cases. It increases dopamine receptors in central nervous system. Additionally it is used for suppression of lactation, hypogonadism, galactorrhoea and in cyclical benign breast and menstrual disorders[5]. It is given in doses of 1.25mg orally at night followed by 2.5 mg a night after 2-3 days and then 2.5 mg twice daily afterwards to be taken with food. Its side effects include occasional vomiting, dizziness, postural hypotension, syncope, headache and rarely gut bleeding tendency.

2. Primary hypothalamic failure

Absence or deficiency of luteinising hormone -releasing hormone (LHRH) reachingthe pituitary, results in the depressed gonadotrophin and oestrogen levels and failure of ovulation. Evidence of ovulation will be lacking, e.g., absence of a basal body temperature shift at the midcycle and absence of changes in consistency and penetrability of cervical mucus by spermatozoa. This is characterised by the hypogonadotrophic hypogonadism of hypothalamic origin which occurs in Kelmann's Syndrome (anosmia with gonadal failure). This syndrome is congenital and the mode of inheritance is probably dominantly autosomal as it has shown father-to-son transmission. Autopsy histological findings in this condition reveal olfactory bulb aplasia, normal pituitary gland, hypoplasia of hypothalamus and low baseline levels of gonado trophic hormones (LH and FSH). Patients are traditionally treated with

exogenous gonadotrophins[6] but these are expensive and rather difficult to use, since adequate but not excessive doses must be established. More recently[7,8] use of LHRH in cases of primary hypothalamic failure in a pulsatile fashion at specific days of the cycle has achieved a sequence of complete and fertile cycles. Pregnancy can ensue at a high rate and can proceed to a successful therapy.

3. Hypothalamo-pitultary failure

Aetiology of this condition is not well defined. However, hypothalamo-pituitary failure is characterised by an insufficient secretion of gonadotrophin to produce full reproductive cycles. Oestrogen levels may fail to rise fully and also fail to decline at various days of the cycle. Rather, oestrogen concentration remains at slightly elevated levels throughout an anovulatory cycle. TJltrasonography of the ovary reveals antral follicles that fail to mature. Gonadotrophin or clomiphcne therapy in these cases may be useful:

(i) Gonadotrophin therapy: The condition can be treated successfully in some cases by therapy with exogenous FSH to maintain or improve follicular growth and oestrogen output; if an endogenous LH[9] surge does not occur or is weak, it can be supplemented with exogenous LIP. However, correct doses of FSH are difficult to adjust as slight overdosage may cause hyperstimulation leading to multiple ovulation and multiple implantation.

(ii) Clomiphene therapy (Clomid): Clomiphene citrate is the most widely used drug to induce ovulation. It is an anti-oestrogenic nonsteroid compound. The effectiveness of clomiphene in the induction of ovulation for fertility is well established. Its structural similarity to an oestrogenic substance (diethyIstilbestrol) gives the clue to the mechanism of action. It is believed that clomiphene acts primarily on the hypothalamic centre by competitively binding for oestrogen receptors preventing the transmission of an oestrogenic message to thenucleus of the hypothalamic cells[10]. Owing to the negative feedback system, LHRH is secreted and, in turn, the pituitary secretes FSH and LH. This increase in FSH stimulates follicular maturation which induces an increased production of oestradiol. By the positive feedback effect of oestradiol, an ovulatory surge of FSH and LH occurs. Ovulation usually occurs 5 to 11 days after the completion of clomiphene therapy[11,12]. The dosage required to induce ovulation varies widely. However, one usually starts with a dose of 50 mg daily for 5 days. If the patient responds by showing ovulatory evidence, this dosage should be maintained for at least 6 months. However, if ovulation does not occur, the daily dosage should be increased by 50 mg (1 tab) each cycle up to as high as 200 mgaday for 5 days. The patient should record her basal body temperature and should be examined before each treatment cycle for the possible ovarian enlargement. In the properly selected patients, 80% of the treated patients can be expected to ovulate and approximately 50% become pregnant with the clomiphene therapy. The incidence of multiple birth mostly twins is 6 to 8%. The abortion rate is about 20% and the side-effects seem to be dose-related. The common problems are hyperstimulation of the ovaries, hot flushes, abdominal discomfort, nausea and transient alopecia[13].

Defects of follicle maturation

Defective follicular maturation is seen in polycystic ovarian disease (PCO). PCO is a heterozygous disorder with varying clini cal features like obesity, menstrual irregularities, hirsutism and infertility[14]. The syndrome includes various underlying biochemical and physiological defects. Its aetiologyis poorly understood. This syndrome is generally characterised by elevated gonadotrophins, low urinary oestrogens, elevated ovarian androgens output and little aromatisation of androgens. Furthermore, follicles are rendered unresponsive to gonadotrophins and ultrasonographic studies reveal failure to detect mature ovarian follicles. A diagnostic laparoscopy maybe indicated only when clinical assessment of ovarian status is uncertain. The possthle lines of treatment include:

(i) Corticosteroid treatment: It is the treatment of choice when PCO is caused by ACTH- dependent adrenocortical hyperfunction. Rather small doses (prednisone 5 to 10 mg daily or dexamethasone 0.5 to

1 mg daily) usually suppress androgens of adrenal origin[15].

(ii) Clomiphene citrate (Clomid): This antioestrogenic non-steroid compound in a dose of 50-100 mg daily for 6 months has proved successful in 50% of cases result ingin ovulation followed by pregnancy[16]. .~“

(iii) LH/FSH or LHRH therapy: Gonadotrophin, LHRH or even human menopausal gonadotrophin (HMG) have been of little use with serious side-effects in cases of polycystic ovaries[17].

(iv) Wedge resection: Surgical intervention (wedge resection of ovaries) in selected cases of PCO have been found successful. Almost one half of these “successful’ patients can have recurrence of the manifestation[18] of PCO. For these reasons, it should be considered only for those patients who tried to conceive and failed on clomid therapy. It has been observed that wedge resection reduces the plasma levels of androgens transiently.

5. Effects of disorders of ovulation

The major effects produced due to the various disorders of ovulation discussed above include

(1) anovulatory cycles,

(2) abbreviated luteal phase.

1. Anovulatory cycles: Anovulation is the key feature of this condition and presents as amenorrhoea in approximately 55% of cases and with irregular heavy bleeding in 28%. True virilisation is rare, but 70% of anovulatory patients complain of cosmetically disturbing hirsutism. The development of hirsutism depends not only on the concentration of androgens in the blood but on the genetic sensitivity of hair follicles to androgens. Obesity has been classically regarded as an important feature, but in view of the concept of persistent anovulation arising from many causes, its presence is extremely variable and has no diagnostic value[19]. While an elevated LH value in the presence of a low or low-normal FSH may be diagnostic, the diagnosis can easily be made by the clinical presentation alone. Indeed, the androgen impact may be such that the oestrogen-induced LH secretion is suppressed. About 10-20% of patients with this condition do not have elevated LH levels with reversal of the LH/FSH ratio. Besides the problems of bleeding, amenorrhoea, hirsutism and infertility, the effect of unopposed and uninterrupted oestrogen is to place the patient in considerable risk of cancer of the endometrium and cancer of the breast[20]? If left unattended, patients in the persistent anovulation develop problems and therefore, appropriate therapeutic management is essential for all anovulatory patients. The typical patient presents with anovulation and irregular menstruation or amenorrhoea with withdrawal bleeding after a progestational challenge. If there is no hirsutism or virilism, evaluation of androgen production is not necessary. There is no need for urinary 1 7-ketosteroids, blood testosterone, blood dehydroepiandros terone (DHEAS) or any other laboratory procedures. Therapy of most anovulatory patients can be planned at the first visit. If the patient desires pregnancy, she is a candidate for the medical induction of ovulation. If the patient presents with amenorrhoea, an investigation must be pursued. For the patient who does not wish to become pregnant and does not complain of hirsutism, but is anovulatory and has irregular bleeding, therapy is directed towards the interruption of the steady state effect on the endometrium and breast. The use of provera (10 mg daily for the first 10 days of every month) is favoured to ensure complete withdrawal bleeding and to prevent endometrial hyperplasia[21]. The monthly 10 days duration therapy has been shown to be essential to protect the endometrium from cancer in women on oestrogen replacement therapy. Until specific clinical data are available, it seems logical that young, anovulatory women also require 10 days of gestational exposure every month. The use of oral contraception medication for therapy in these patients requires individual patient judgement. In our opinion, when reliable contraception is essential, the use of low dose combination oral contraception in the usual cyclic fashion is appropriate. As an ultimate measure, the remedy in this condition is to recover oocyte from the follicles laparoscopically in women and to attempt in vitro fertiisation, if pregnancy is required. Abbreviated luteal phase: Progesterone levels normally rise sharply after ovulation reaching a peak approximately 8 days after the LH surge. Progesterone acts both

locally and centrally to suppress the new follicular growth[22]. Because progesterone antagonises oestrogen action (through depletion of oestrogen receptors), it is not surprising that oestro gen-dependent follicular mechanisms may be inhibited[23]. Inhibition of new follicular growth during the luteal phase is further inhibited by the low levels of gonadotrophins due to the negative feedback actions of both oestrogen and progesterone. Under normal circumstances, therefore, a woman probably ovulates from alternate sides. This mechanism obviously cannot be over whelmed when only one ovary is present. Some women with apparently normal ovulations, nonetheless, show slow or reduced rises in progesterone and this is associated with infertility. Such a pattern is also observed quite frequently in women that have undergone clomiphene[24] or bromocriptine therapy and may therefore represent some deficiency in the maturation of granulosa cell, that is manifested by poor luteinisation; for example, inadequate development of LII or prolactin receptors. However, the precise cause of luteal inadequacy remains uncertain and since it is not yet clear whether in women either LII or prolactin are luteotrophic, a deficiency in these cases cannot be invoked by way of explanation. Progesterone therapy has been of little use for these problems[25].

REFERENCES

1. Soong. Y.K., Ferguson, K.M., McGrarrick, 0. and Jeffcoat, S.L Size heterogenecity of immunoreactive prolactin in byperprolacti naemic serum. Clin. EndocrinoL, 1982; 16:259.
2. Frantz, AG. The regulation of prolactin secretion in humans, in Frontiers in neuroendocrinology. Editedby W.F. Ganongand L Martini. Oxford, Oxford University Press, 1973, p.337.
3. Kredentser, J.V., Hoskin, CF.and Scoot, J.Z. Hyperprolactinse mis -a significsntfactor in female infertility. Am.). Obstet. Gynaecol., 1981; 139:264.
4. Bartrieri, RL and Ryan, K.). Bromocriptine: Endocrinepharma cology and therapeutic application. Fertil. SteriL, 1983; 39:727.
5. Moult, P3., Rees, L.H. and Besser, G.M. Pulsatile gonadotrophin secretion in hyperprolactinsemic amenorrhoea and the response to bromocriptine therapy. Gin. EndocrinoL, 1982; 16:153.
6. Messinis, I.E. and Templeton, A.A. Pituitasy response to exoge nous LHRH in superovulatedwomen.). Reprod. Fert., 1989; 87:633.
7. Aslam, M., Luteinising hormone. relessing hormone and its gynae cological applies. tions. Pakistan Armed Forces Med.)., 1988; 41:25.
8. Stearin, G., Nillius, Si. and Wide, L Pulsatile low dose LHRH treatment for induction of follicular maturation and ovulation in women with anaesthesia. Acts EndocrinoL, 1982; 107:78.
9. Beltendorf, G., Braendle, W. and Sprotte, Ch. Overall results ofgonadotrophin therapy in advance diagnosis and treatmentof infertility. Edited by V. lnslerand G. Bettendorf. New York, Elsevier, 1981, p.21.
10. Marshal,).C. Amenorrhoea. Medicine, 1989; 64:2649.
11. Talbert, M.D. clomiphene citrate- induction of ovulation. Fer til. Steril., 1983; 39:6.
12. Messinis, I.E. and Templeton, A Blockade of the positive feed back effect of oestradiol during prolonged administration of elomiphene citrate to norms! women. Gin. EndoerinoL, 1988; 29:509.
13. kurachi, K., Aono, T., Minagawa, 3. and Miyake, A Congenital malformations of newborn infants after domiphene-induced ovulation. Fertil. Steril., 1983; 40:187.
14. Jacobs, H.5. and Conway, G.S., Polycysticovary syndrome. Mcdi eine, 1989; 64:2656.
15. efferies, W.M. and Lay, R.P. Treatment of ovarian dysfunction with small doses of cortisone or hydrocortisone. 3. Clin. Endo crinol. Metab., 1959; 1%1069.
16. Lobo, R.A, Paul, W., Msrch, CM., Grsnger, L and Kletzky, O.K. Clomiphene and dexamethasone in women unresponsive to clomiphene alone. Obstet. Gynaecol., 198Z 60:497.
17. Taymor, M.L Induction of ovulation with gonadotrophins. Clin. Obstet. GynaeeoL 1973; 16:201.

18. Lunde, 0. Polycystic ovarian syndrome; a retrospeetivestudyof the therspeuticeffectof ovarian wedge resection after unsuc cessful trestment with elomiphene citrate. Ann. Gin. GynaecoL. 1982; 71:330.
19. Prunty, F.T. Hirsutism, virilism and apparent virilism snd their gonadal relationships.). Endocrinol., 1967; 38:203.
20. Cowan, LD., Gordis, L, Tonsseis,).A and)ones, G.S. Breast cancer incidence in women with a history of progesterone deficiency. Am.). EpidemioL, 1981; 114:209.
20. Pardthaisong, T., Gray, RH. and McDaniel, LB. Return of fertility after diseontinustion of depot medroxyprogesterone acetate and intrauterine devices in Northern Thailand. Lancet, 1980; 1:509.
22. Rosenfeld, DL, Chudow, S. and Bronson, R.A Diagnosis of luteal phase inefficiency. Obstet. Gynaecoi, 1980; 56:193.
23. Hsueh, A).W., Peck, E.J. and Clark,).H. Progesterone antagonism of the oestrogen receptor sod oestrogen-induced uterinegrowtb. Nature, 1975; 254:337.
24. Talbert, M.D. Clomiphene citrate- Induction of ovulation. Fer tiL SteriL, 1983; 39:6.
25. DiZeregs, G.S. and Hodgen, G.D. The interovarian progesteronegradient;a spatialand temporal regulator of folliculogenesis in the primate ovarian cycle. J. Gin. EndoerinoL Metab., 1982; 54:495.