ADULT ONSET AMENORRHOEA, ETIOLOGY AND PROGNOSIS

KAMALINI DAS • MANORAMA SINGH

SUMMARY

A series of 84 patients with amenorrhoea of adult onset were studied. The commonest cause was found to be due to Polycystic Ovarian disease (31%). The other important causes in order of frequency were Primary Ovarian failure (21%). Uterine and hypothalamic causes (14%). Hyperprolactinaemia (12%) and Endocrine causes (7%). Ovulation, abortion and conception rates of patients with treatment directed primarily towards ovulation induction were found to be 100%, 17% and 67.6% respectively, if patients with ovarian and uterine causes of amenorrhoea were excluded. The prognosis for future fertility for patients with adult onset amenorrhoea was found to be better than that reported for patients whose amenorrhoea was a result of pubertal aberrancy.

Introduction

Secondary amenorrhoea is not uncommon problem in India. Not only do these women suffer from infertility, but they also have to bear the social stigma associated with this condition. Differentiation from Primary amenorrhoea is important as it would exclude genetic and chromosomal causes of amenorrhoea. Adult onset or Late onset amenorrhoea, a term coined by Reindollar R.H. in 1986 includes those whomen who developed amenorrhoea lasting for at least six months before the age of 39 years preceded by at least 6 menstrual periods after menarche. This definition was used in this study to define the study group, as it more definitely excluded thoses cases due to pubertal abberancy. There are not many studies from India on adult onset amenorrhoea, the etiology and prognosis of which would vary from that described in western literature. This study describes our experience with 84 patients with Adult onset amenorrhoea.

The Department of Obstetrics and Gynaecology, Safdarjung Hospital, New Delhi 110 029.

Materials and Methods

Over the period of 1 year, 84 women who presented to the outpatient clinic of Safdarjung Hospital with Adult onset amenorrhoea, formed the study group. The criteria for inclusion was amenorrhoea of at least 6 months duration developing in the reproductive years preceded by at least 6 or more periods after menarche. A de-

tailed history and physical examination with special reference to psychological factors, stress, dietary habits, drugs and thyroid dysfunction was done. All women fulfilling the above criteria were given medroxyprogesterone acetate 5 mg daily for 5 days, and estrogen and progesterone pills as oral contraceptives to those women with no withdrawal with progesterone alone. Women who failed to respond to estrogen and progesterone withdrawal were investigated for uterine factors.

The ramaining patients had FSH, LH, prolactin and thyroid function estimation done. X-ray skull and CT scan were done when indicated or serum prolactin was high. They also underwent a pelvic ultrasound to determine the uterine and ovarian index. (Tan S.L. 1985). Diagnostic laparoscopy was required only in few cases of primary ovarian failure.

Women with a positive progesterone withdrawal were treated with clomiphene 50 mg daily for 5 days starting from the 2nd day of the cycle. This dose was increased in each cycle upto a maximum of 200 mg daily for 5 days or till the patient had evidence of ovulation on the BBT and a good midcyclic cervical mucus score. Dexamethasone 0.5 mg daily was added to clomiphene if serum LH was more than 30mIU/ml. (Rajan 1988). If these women did not ovulate with the above regime and serum prolactin was elevated, they were trated with Bromocryptine with or without clomiphene.

Women with a negative progesterone withdrawal test were managed according to the serum FSH, if greater than 40mIU/ml they were diagnosed as cases of primary ovarian failure and put on low dose estrogen and progesterone replacement. (O : Herlihy. C. 1980). The rest of the patients in this group were treated with Bromocryptine if serum prolactin was high, and HMG and HCG if serum prolactin was in the normal range.

During induction of ovulation patients were followed up with regular BBT charts and midcycle cervical mucous scoring. Only one patient on gonadotrophin treatment was able to afford ultrasound monitoring of follicles during induction.

Patients with hypothyroidism were treated with eltroxin. 2 patients with thyrotoxicosis were treated with Neomercazole. Endometrial Biopsy was done for those patients with a uterine cause of amenorrhoea, to rule out genital tuberculosis, and hysterosalpingogram was done when the histopathology was negative for tuberculosis. All patients were followed up for a period of 2 years.

Results

The etiological factors in adult onset amenorrhoea in this study are shown in Table I. The commonest cause was found to be polycystic ovarian disease (31%) this is due to a deranged positive feedback to the hypothalamus. Primary ovarian failure diagnosed by an FSH greater than 40mIU/ml was seen in 21% of cases. Patients developing primary Ovarian failure before the age of 30 years were more likely to have chromosomal anomalies, primary infertility and a negative family history, as compared to those developing primary ovrian failure after 30 years of age. Table II. All these patients were put on cyclical estrogen and progesterone, but one developed spontaneous menstruation or ovulation during the follow up period.

Hypogonadotrophic amenorrhoea accounted for 14% of cases. The etiology of this type of amenorrhoea is shown in Table

TABLE - I
ETIOLOGY OF ADUOL ONSET AMENORRHOEA

Etiology	Number	%	Diagnosis	No.	Treatment
1. Deranged positive feed-back	26	31	PCOD	12	Clomiphene CC
			PCOD with Androgen excess	10	CC + Dex.
2. Primary Ovarian Failure	18	21	POF <30 years	10	E + P
			Premature sp. Menopous >30 years	8	E + P
3. Uterine Factor	12	14	Tubercular Endometritis	9	ATT
			Ashermans syndrome	3	Lysis + Loop + E + P
4. Hypogonadotrophic Amenorrhoea	12	14	O.C. induced	1	HMG + HCG
			post delivery	8	
			Unknown	3	
5. Hyperprolactinemia	10	12	Microadenoma	2	Bromocryptine
			Idioathic	8	Bromocryptine
6. Endocrine Disorder	6	7	Hypothyroidism	4	Eltroxin
			Hyperthyroidism	2	Neomercazole

TABLE - II
FACTORS ASSOCIATED WITH PRIMARY OVARIAN FAILURE

Time of Onset	Number	Family History	Chromosomal Abnormalities	Infertility		Conception with Treatment
				Primary	Secondary	
Before 30 years	10	—	3	8	2	—
After 30 years	8	6	—	—	1	—

III. The commonest cause of this amenorrhoea was following delivery and prolonged lactation for 3 to 5 years when amenorrhoea persisted even after discountinuing lactation. Serum prolactin in these patients was normal and this amenorrhoea may reflect the stress of child rearing, nutritional factors or an early subclinical pituitary microadenoma. 2 of these patients presented with early regression of lactation, were clinically anaemic and thyroid function tests adrenal functions were low normal. These two patients may have been cases of mild early post partum pituitary necrosis. This could have been established by a GNRH Stimulation test.

Uterine factors were implicated in 14% of cases. Table IV. 9 were found on

TABLE - III
HYPOGONADOTROPHIC AMENORRHOEA

Diagnosis		Etiology	Number
1.	Oral contraceptive induced	Hypothalamic Supression	1
2.	Post Delivery	Nutritional*	2
		Stress*	4
		Post partum pituitary Necrosis	2
		? Subclinical microadenoma	—
3.	Unknown	? Stress	3
		? Drug induced	
4.	Anorexia Nervosa	Hypothalamic Supression	—

* Both may be associated factors in the development of amenorrhoea.
** Serum Prolactin was normal in all cases.

endometrial biopsy to have genital tuberculosis, and were put on antitubercular treatment with Rifampicin, Isoniazid, and streptomycin for 8 months. 2 had scanty spontaneous menstruation on treatment, but none conceived during the 2 years follow up period. Of 3 patient with Ashermans syndrome, only one was interested in conception and underwent lysis of adhesions, lippes loop insertion, and was put on oral contraceptives, on which she developed regular menstruation. The other two patients when explained the reason for amenorrhoea chose not to have further treatment.

Ovulation, abortion and pregnancy rates for the remaining 34 patients who were keen on conception is shown in Table V with the method of treatment given, all patients showed evidence of ovulation on BBT and cervical mucous scoring. Only one patient on HMG and HCG treatment was followed up with ultrasound examination for follicular development and she conceived in the 2nd treatment cycle. The remaining 23 conceptions were within 3-6 months of treatment. Only 2 patients required a change of regime and conceived after a further 2 months of treatment. The abortion rate was 17.4% only slightly

TABLE - IV
UTERINE FACTORS IN ADULT ONSET AMENORRHOEA

Diagnosis	Number	Infertility		Treatment	Conception
		Primary	Secondary		
Tb. Endometritis	9	4	2	ATT	—
Ashermans	3	—	1	lysis+loop Estrogen+ Progestrone	—

higher than the value in the normal population of 10-15%. The overall full term pregnancy rate in 8 months of treatment was 55.9%. The conception rate being 67.6%.

TABLE - V
OUTCOME OF INDUCTION OF OVULATION IN 34 PATIENTS

Treatment	Number	Ovulation	Abortion	Term of continuing pregnancy
Clomiphene (CC)	6	All	1	4
Clomiphene + Dexa	11	All	2	8
CC + HCG	4	All	1	1
Bromocryptine	6	All	—	3*
HMG + HCG	5	All	—	1
Neomercazole	2	All	—	2

* One patient required CC with Bromocryptine for ovulation and conception.

Discussion

The etiological factors in adult onset amenorrhoea in this study and that of Reindollar 1986 differ significantly. Table VI. Hypothalamic causes associated with weight loss accounted for more than 50% of their patients compared to weight loss being an associated factor for only 2 patients in this study. Table III. Further more the weight loss in their study was due to anorexia nervosa and associated with primary infertility, compare to that developing after delivery in this study. This may reflect the low socioeconomic status of the patients attending the Safdarjung Hospital outpatient department, but it also indicates the rarity of amenorrhoea due to anorexia nervosa in this country. Tuberculous endometritis accounted for 10.7% of cases in this study. The incidence of primary ovarian failure was higher, 21% than that recorded by Franks in 1987 of 11%.

TABLE - VI
COMPARISON OF ETIOLOGIC FACTORS IN ADULT ONSET AMENORRHOEA

Etiology		Reindollar	Franks	Present Study
1.	Weight Loss (Anorexia Nervosa)	30%	35%	2.4%
2.	Polycystic Ovarian Disease	28%	32%	31%
3.	Primary Ovarian Failure	12%	11%	21%
4.	Hyperprolactinaemia	15%	11%	11.9%
5.	Hypogonadotrophine amenorrhoea (not related to wt loss)	5%	9%	11.9%
6.	Uterine Cause	7%	2%	14.28%
7.	Thyroid Dysfunction	-3%	—	7.14%

Ovarian and uterine causes of amenorrhoea have been found in this study to have a dismal prognosis for future fertility. Table II and Table IV. Hagre WM 1987 and Oherlinhy 1980, have found spontaneous ovulation rates of 17% and 25% respectively in patients which hypergonadotrophic amenorrhoea. This may be because an FSH of 20mIU/ml was used the cut-off point for the diagnosis of primary ovarian failure in their study as compared to 40mIU/ml in the present study. An attempt was made to induce ovulation with clomiphene for some of these patients with no evidence of menstruation or ovulation. Jerome 1984 and Fleming 1984 have recorded pregnancies in patients with primary ovarian failure treatment with estrogen and HMG and GNRH respectively. We did not try inducing our patients with the above regime. Excluding ovarian and uterine causes of amenorrhoea, ovulation could be induced in all patients with a conception rte of 67.6% by the end of 8 treatment cycles, with 55.9% of patients going upto term pregnancy. Pregnancy rates of 93% have been reported by Hull 1979 using ultrasound studies and radioimmunoassay techniques in following follicular maturation. Table VII.Even with methods such as BBT and cervical mucous scoring, pregnancy rates of 67.6% could be achieved, which could be further enhanced by using sophisticated methods for monitoring the follicle (Charles M. 1987). The lower overall pregnancy rates in this study may be as a consequence of the higher percentage of women with tubercular endometritis and primary ovarian failure both with a poor prognosis for fertility. With newer and shorter four drug regimes for tuberculosis using Rifampicin there is some hope for better pregnancy rates in these women. (O'Herlinhy C. 1979) Ovum or embryo donation techniques have brightened the childbearing prospects of women with primary ovarian failure (Lutgen 1985).

Since 95% of the estradiol produced in a woman is secreted by the dominant follicle, a patient with amenorrhoea runs the risk of estrogen dificiency and thus patients with untreatable, secondary amenorrhoea like primary ovarian failure, should be put on long term low dose replacement steroids, to avoid the early and late effects of estrogen deficiency.

Conclusion

Following a simple format for the diagnosis of adult onset amenorrhoea, and treatment directed primarly towards induction of ovulation, the prospects for future childbearing is only slightly lower than that for spontaneously ovulating women. There is also a wide scope for improvement of the pregnancy rate with more sophisticated methods of monitoring of the follicle.

TABLE - VII
COMPARISION OF PREGNANCY RATES IN ADULT ONSET AMENORRHOEA

Study	Ovulation Rate	Conception Rate	Abortion Rate	Term Pregnancy Rate
Hull	100%	93%	22%	—
Present Study	100%	67.6%	17.4%	55.9%

References

1. *Charles M. March : Am. J. Obstet. Gynecol. 156:1473, 1987.*
2. *Fleming R., Hamilton M.P.R., Barloco D.H., Cordines J.W., Coults J.R.T.: Lancet 1:1473, 1984.*
3. *Franks S.: Br. Med. J. (Clin Res.) 294:815, 1987.*
4. *Hagrew M.W., Tan S.L., Adam J., Jacobs H.S.: Int. J. Gynec. Obstet. 25:121, 1987.*
5. *Hull M.G.R., Savage P.E., Jacobs H.S.: Br. Med. J. 1:1257, 1979.*
6. *Jerome H. Check, Jeffery S. Chase : Fertile, Sterile, 46:919, 1984.*
7. *Lutjen P., Trounson A., Lecton J., Findlay J., Wood C., Renou P.: Nature 307:174, 1985.*
8. *O'Herlinhy C.: Acta Obstet. Gynec. Scan. 58:57, 1979.*
9. *O'Herlinhy C., Pepperell R.J., Evans J.H.: Br. Med. J. 281:1447, 1980.*
10. *Rajan R.: Postgraduate Reproductive Endocrinology. 1st Edition, Published by the Infertility Commttee of Federation of Obstetrics and Gynaecological Societies of India. Page 399.*
11. *Reindollar R.H., Michael Novak, Sandra D.O., Tho P.T., Paul G., McDonough M.D.: Am.J. Obstet. Gynec. 155:531, 1986.*
12. *Tan S.L., Jacobs H.S.: Clin. Obstet. Gynec. 12:725, 1986.*