USE OF ALGORITHMIC APPROACH TO EVALUATE THE CAUSE OF SECONDARY AMENORRHEA

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ABSTRACT: Secondary amenorrhea in women of reproductive age may be an indication of an undiagnosed, chronic condition and appropriate treatment is dependent upon accurate diagnosis of the underlying etiology. A thorough clinical assessment and a few common laboratory tests can easily identify the most frequent causes of secondary amenorrhea. However in these cases, misdiagnosis is unfortunately common and often the result of poor laboratory utilization in the form of a failure to employ indicated tests, the use of obsolete tests, or erroneous interpretation in the face of interfering factors or co-morbidities. Consequently, the algorithmic approach to laboratory evaluation in the context of secondary amenorrhea described in this review can minimize the risk of diagnostic error as well was decrease test volume, cost, and time to diagnosis.aim of the study is to evaluate the cause of secondary amenorrhea using an algorithmic approach. 100 cases were selected randomly among patients of secondary amenorrhea who gynaecological OPD of DMCH Laheraisarai.

KEY WORDS: secondary amenorrhea, algorithmic approach

INTRODUCTION: Secondary amenorrhea is defined as a failure of menses to appear for 3 cycles or for 6 months or more following initial normal menstrual function[1]. In females of reproductive age, diagnosing amenorrhea is a matter of first determining whether pregnancy is the etiology. In the absence of pregnancy, the challenge is to determine the exact cause of absent menses[2]. It can result from a simple cause like temporary psychic stress or may be the first signal of a serious underlying disease like pituitary tumor. The differential diagnosis of secondary amenorrhea is broad. To facilitate prompt and accurate diagnostic work up obtaining a thorough history and performing detailed physical examination is essential. Then an algorithmic approach is followed to narrow the diagnostic possibilities. This kind of systematic approach avoids unnecessary and expensive diagnostic procedures.

Materials and Method: 100 cases of secondary amenorrhea who attended gynaecological OPD of Darbhanga Medical College & Hospital, Laheriasarai, Bihar, were the subjects of the present study. Duration of study was from March 2010 to August 2011.

- Age group was 16 – 40 years.
- Duration of secondary amenorrhea was at least 6 months or more.
- Cases having secondary amenorrhea due to obstetrical cause were excluded from the study.
- After adequate history taking and meticulous physical examination cases were investigated according to the following flow chart.

WORK UP: As illustrated in the flow chart below (figure 1).

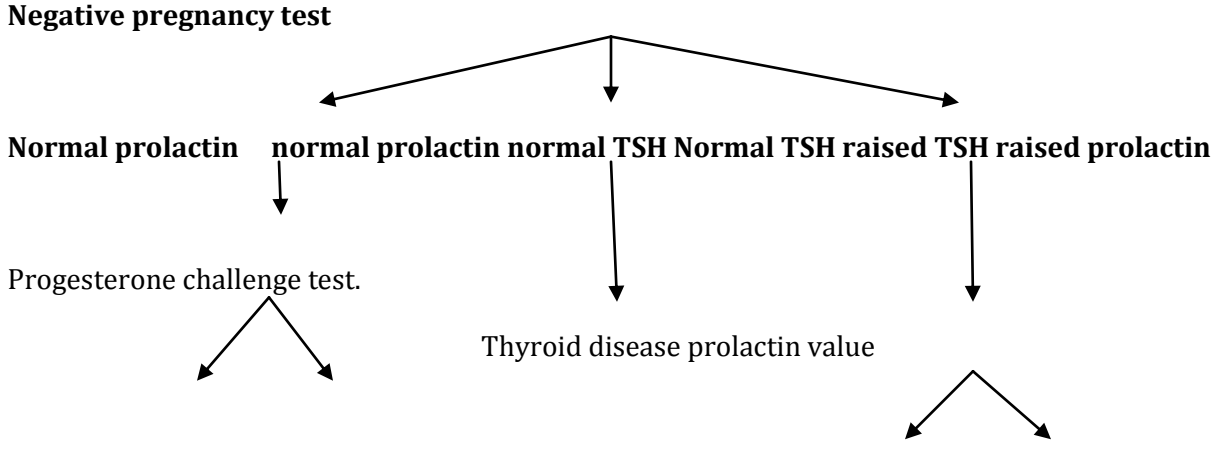
After pregnancy is ruled out, the initial work-up should be based on patient history and physical examination findings (Table 1). Prolactin and TSH levels should be checked in all patients.

If TSH and prolactin levels are normal, a progestogen challenge test (Table 2[3,4]) can help evaluate for a patent outflow tract and detect endogenous estrogen that is affecting the endometrium. A withdrawal bleed usually occurs two to seven days after the challenge test [3]. A negative progestogen challenge test signifies an outflow tract abnormality or inadequate oestrogenization. An estrogen/progestogen challenge test (Table 2 [3,4]) can differentiate the two diagnoses. A negative estrogen/progestogen challenge test typically indicates an outflow tract obstruction. A positive test indicates an abnormality within the hypothalamic-pituitary axis or the ovaries. Gonadotropin levels can further help determine the source of the abnormality. Elevated follicle-stimulating hormone (FSH) or luteinizing hormone (LH) levels suggest an ovarian abnormality (hypergonadotropic hypogonadism). Normal or low FSH or LH levels suggest a pituitary or hypothalamic abnormality (hypogonadotropic hypogonadism). Magnetic resonance imaging (MRI) of the sella turcica can rule out a pituitary tumor. Normal MRI indicates a hypothalamic cause of amenorrhea [3].

In my clinical study I have used Medroxyprogesterone acetate (Provera) 10 mg orally once per day for 7 days (as Progestogen challenge test) and Conjugated equine estrogen (Premarin) 1.25 mg orally once per day for 21days followed by progesterone as stated above (as Estrogen/progestogen challenge test), but other options are also available for Progestogen challenge test and Estrogen/progestogen challenge test as mentioned in the table below (table 2).

Flowchart

Patient presenting with secondary amenorrhea



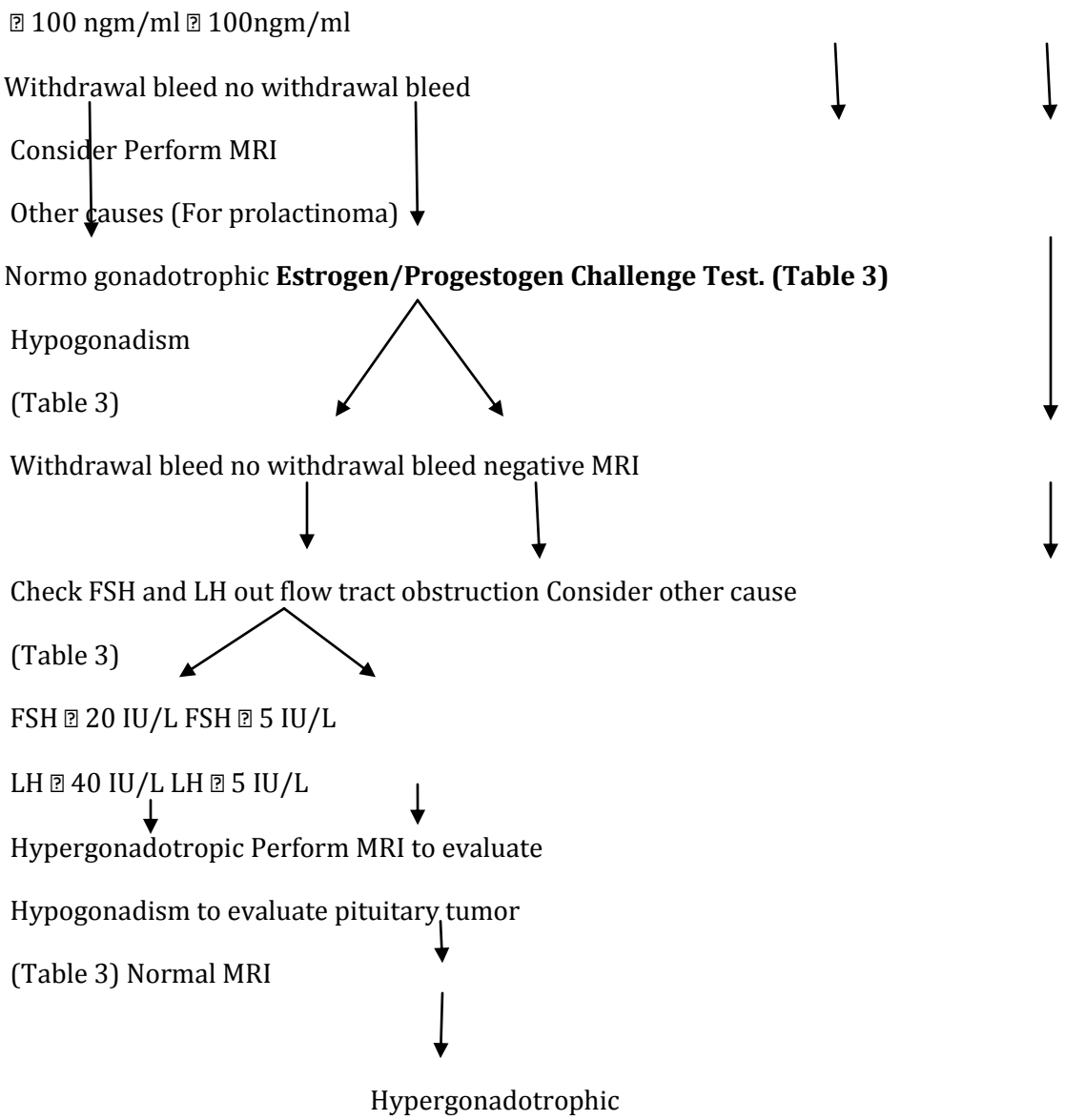


FIGURE 1: [3,5,6,7] is an algorithm for evaluation of secondary amenorrhea.

TABLE 1: History and Physical Examination Findings Associated with Amenorrhea. [6, 7]

Findings	Associations
Patient history	
Exercise, weight loss, current or previous chronic illness, illicit drug use	Hypothalamic amenorrhea
Prescription drug use	Multiple, depending on medication
Previous central nervous system chemotherapy or radiation	Hypothalamic amenorrhea
Previous pelvic radiation	Premature ovarian failure
Psychosocial stressors; nutritional and exercise history	Anorexia or bulimia nervosa
Physical examination	
Body mass index	Polycystic Ovary syndrome
Striae, buffalo hump, significant central obesity, easy bruising, hypertension, or proximal muscle weakness	Cushing's disease
Thyroid examination	Thyroid disease
Galactorrhea; headache and visual disturbances	Pituitary tumor
Hirsutism or acne	Polycystic ovary syndrome
Signs and symptoms of hypothyroidism or hyperthyroidism	Thyroid disease
Vasomotor symptoms	Premature Ovarian failure

TABLE 2: Guidelines for Progestogen and Estrogen/Progestogen Challenge Tests. [3, 4]

Drug	Dosing	Duration
Progestogen challenge test		
Medroxyprogesterone acetate (Provera)	10 mg orally once per day	Seven to 10 days
Norethindrone (Aygestin)	5 mg orally once per day	Seven to 10 days
Progesterone	200 mg parenterally once per day	Single dose
Progesterone micronized	400 mg orally once per day	Seven to 10 days
Progesterone micronized gel (4 or 8%)	Intravaginally every other day	Six applications
Estrogen/progestogen challenge test		
Conjugated equine estrogen (Premarin)	1.25 mg orally once per day	21 days
Or		
Estradiol (Estrace)	2 mg orally once per day	21 days
followed by		
Progestational agent	As noted above	As noted above

TABLE 3: Causes of Amenorrhea. [3,7,8]

Ectopic production
Breastfeeding
Breast stimulation
Hypothyroidism
Medications
Empty sella syndrome
Pituitary adenoma
Autoimmune
Chemotherapy
Galactosemia
Genetic
17-hydroxylase deficiency syndrome
Idiopathic
Mumps
Pelvic radiation
Chronic liver disease
Chronic renal insufficiency
Diabetes
Immunodeficiency
Inflammatory bowel disease
Thyroid disease
Severe depression or psychosocial stressors
Acromegaly
Androgen-secreting tumor (ovarian or adrenal)
Cushing's disease
Exogenous androgens
Polycystic ovary syndrome
Thyroid disease
Asherman's syndrome
Cervical stenosis

RESULTS: In my study out of 100 patients of secondary amenorrhea, 38 cases were in the age group of 30 – 39 years, 52 cases were in the age group of 20 – 29 years, and rest 10 cases were less than 19 years.

Base line serum prolactin and TSH were performed in all patients. 7 case showed hypothyroidism. 25 cases had elevated serum prolactin level. Out of these 25 cases 7 cases had serum prolactin level ? 100 ng/ dl. These cases when subjected to MRI showed presence of prolactinoma. Out of these 25 cases 7 cases had associated hypothyroidism, 9 cases had history of drug use and 1 case was a diagnosed case of chronic renal failure. 1 case with no other abnormality other than hyperprolactinemia was found was assumed to be temporary stress related.

Those with normal serum prolactin and TSH were subjected to Progestogen challenge test. Out of 75 cases 53 cases had positive withdrawal bleeding.

Of these 53 cases 20 cases were diagnosed as PCOS based on clinical features and laboratory investigations. 33 cases with positive to Progestogen challenge test when further investigated (endometrial biopsy) were found to have genital tuberculosis.

Those with negative progestogen challenge test (22 cases) were subjected to estrogen/progestogen challenge test. 16 cases had positive withdrawal bleeding and were subjected to serum gonadotrophin estimation. 15 cases had elevated serum FSH and LH and on further investigation were diagnosed as premature ovarian failure. 1 case had very low levels of serum FSH and LH, and was diagnosed as sheehans syndrome based on history and clinical findings.

6 cases with negative estrogen/progestogen challenge test had outflow tract obstruction, 4 cases had Asherman syndrome due to previous dilatation and curettage (D&C) and 2 cases had tuberculous endometritis.

DISCUSSION: The study shows that majority of patients (52%) were less than 30 years of age. Similar results were observed by Baker ER et al 1981[9] according to whom incidence of amenorrhea was higher in females less than 30 years of age. This can be attributed to higher incidence of hyperprolactinemia in younger age group. Exposure to environmental toxins, namely hormonally active endocrine disruptors may also result in increased rates in menstrual and reproductive disorders in endemic areas[10].

The incidence of genital tuberculosis was 35% and it was major cause of secondary amenorrhea in the study. This shows that tuberculosis is an extremely common infection in our country. 33case of genital tuberculosis had positive withdrawal bleeding with progestogen challenge test. Amenorrhea in such cases can be explained by suppression of ovarian function or chronic debility caused by tuberculosis[11]. The any gonadotrophic effect of Mycobacterium tuberculi may be responsible for menstrual irregularities that take place in cases of active pulmonary tuberculosis having no demonstrable lesions in genital tract[12]. 2 cases did not bleed with estrogen/progestogen challenge test. Amenorrhea in such cases was due to endometrial destruction and uterine synechiae formation[13].

PCOS was responsible for 20% cases of secondary amenorrhea. It was the second most common cause of secondary amenorrhea after genital tuberculosis. These patients had clinical features of PCOS like acne, hirsutism, obesity, previous history of oligomenorrhea and laboratory findings of altered LH/FSH ratio, elevated serum testosterone and insulin resistance. Amenorrhea in such cases is explained by chronic anovulation that takes place in PCOS. All these cases had positive withdrawal bleeding with progestogen challenge test showing there by normal endogenous estrogen.

Premature ovarian failure is characterized by amenorrhea, hypoestrogenism, and increased gonadotropin levels occurring before 40 years of age[14]. It was responsible for 15% cases of secondary amenorrhea. Similarly Speroff Et al [15] (1999) reported that premature ovarian failure affects around 10% of cases. There was no history of any radiation exposure or any surgical interference in any of these 15 cases. These cases had elevated serum LH, FSH and low estrogen levels together with menopausal features.

Hypothyroidism was responsible for 7% cases of secondary amenorrhea. These cases also had mildly elevated serum prolactin levels. Previous studies have shown that women with

Hypothyroidism have irregular menses resulting from anovulation [16]. Enhance sensitivity of prolactin secreting cells TRH and defective dopamine turn over resulting in hyperprolactinemia associated with a deficiency of thyroid hormone are the apparent explanation for the associated hyperprolactinemia [17,18,19].

Medication was responsible for 9% cases of secondary amenorrhea, out of which 4 cases had post pill amenorrhea, 3 cases had history of antiepileptic use and 2 cases had history of antipsychotic use.

Prolactinoma was responsible for 7% cases of secondary amenorrhea. These patients had serum prolactin level > 100 ng/ dl together with MRI showing prolactinoma.

1 case was a diagnosed case of chronic renal failure and had amenorrhea due to associated hyperprolactinemia. There was another 1 case in which no other abnormality other than mildly elevated serum prolactin level was found. It was related to temporary stress. It is documented that physiological disturbances, pharmacological agents or markedly compromised renal function may cause elevation in prolactin levels [20]. The cessation of normal ovulatory process resulting from elevated prolactin levels primarily is due to suppressive effects of prolactin via hypothalamic mediation on GnRH pulsatile release [21,22,23].

Asherman's syndrome due to post surgical endometrial scarring was responsible for 4% cases of secondary amenorrhea. All 4 cases give positive history of previous dilatation and curettage (D &C) done. These patients had negative withdrawal bleeding with estrogen and progesterone and HSG showed filling defects. There is formation of uterine adhesions following post abortal and puerperal curettage and also following diagnostic curettage if done vigorously.

Sheehan syndrome is responsible for 1% cases of secondary amenorrhea. There was history of PPH after home delivery. Post delivery she had lactation failure and gradual loss of pubic and axillary hair. Sheehan syndrome is associated with post partum necrosis of the pituitary resulting from a hypotensive episode that, in its severe form (pituitary apoplexy), presents with the patient in shock [24].

TABLE 4: Causes of secondary amenorrhea in study group.

Causes	No. of cases	Percentage
Tuberculosis	35	35
PCOS	20	20
Premature ovarian failure	15	15
Drug induced	9	9
Pituitary tumors	7	7
Hypothyroidism	7	7
Post D & C	4	4
Chronic renal failure	1	1
Sheehan's syndrome	1	1
No pathological factor	1	1
	100	

CONCLUSION: The study shows the important cause of secondary amenorrhea.

The high incidence of genital tuberculosis shows that tuberculosis is a common problem in our country. PCOS is an important cause of menstrual irregularity in young females. In this study hypergonadotropic amenorrhea was mainly due to premature ovarian failure. Hypothyroidism and

hyperprolactinemia are important causes of secondary amenorrhea. It is concluded from the present study that secondary amenorrhea is a challenging problem for the gynecologist and the endocrinologist alike. Sometimes in the hands of an experienced and confident clinician, it also poses problem for its management. Many a times unnecessary costly investigations are carried out to know the cause of secondary amenorrhea. A careful history taking and through physical examination are mandatory before advising any investigation. By systematically investigating the patient (as outlined in the flow chart) unnecessary investigations can be avoided. Thus making the treatment cost-effective and more appropriate.

ABBREVIATIONS:

FSH	:	Follicle stimulating hormone
LH	:	Luteinising hormone
PCOS	:	Polycystic ovarian syndrome
POF	:	Premature ovarian failure
TSH	:	Thyroid stimulating hormone
TRH	:	Thyrotropin Releasing Hormone
HSG	:	Hysterosalpingography
MRI	:	Magnetic Resonance Imaging

REFERENCES:

1. Jeffcoate's principles of gynaecology. 7th edition chapter 37, page 579.
2. Pletcher JR, Slap GB. Menstrual disorders. Amenorrhea. *Pediatr Clin North Am*. Jun 1999; 46(3):505-18.
3. L, Fritz MA. Amenorrhea. In: Clinical gynecologic endocrinology and infertility. 7th ed. Philadelphia, Pa.: Lippincott Williams & Wilkins, 2005; 401–64.
4. Marshall WA, Tanner JM. Variations in patterns of pubertal changes in girls. Arch Dis Child. 1969; 44:291–303.
5. The Practice Committee of the American Society for Reproductive Medicine. Current evaluation of amenorrhea. Fertil Steril. 2004; 82(suppl 1):S33–9.
6. American College of Obstetricians and Gynaecologists. Amenorrhea (ACOG Technical Bulletin 128). Washington, D.C.: ACOG, 1989.
7. Kiningham RB, Apgar BS, Schwenk TL. Evaluation of amenorrhea. Am Fam Physician. 1996; 53:1185–94.
8. Pickett CA. Diagnosis and management of pituitary tumors: recent advances. Prim Care. 2003; 30:765–89.

9. Baker ER, Mathur RS, Kirk RF, Williamson HO. Female runners and secondary amenorrhea; : correlaton with age, parity mileage, and plasma hormonal and sex-hormone-binding globulin concentrations. Fertility and Sterility. 1981; 36(2). 183-7.
10. Phillips KP, Foster WG. Key developments in endocrine disrupter research and human health. *J Toxicol Environ Health B Crit Rev*. Mar 2008; 11(3-4):322-44. [Medline].
11. Jeffcoate's principles of gynaecology. 7th edition *chapter 19, page 327*
12. Jeffcoate's principles of gynaecology. 7th edition *chapter 21, page 361*
13. Dutta DC 5th edition *chapter 10, page 136*
14. Anasti JN. Premature ovarian failure: an update. Fertil Steril. 1998; 70:1–15.
15. Zeon Speroff, Robert H. Glass, Nathon G Kas. Textbook of Clinical Gynecology endocrinology and infertility 6th edition 1999.
16. Krassas GE, Pontikides N , Kaltas T Et al. Disturbances of menstruation in hypothyroidism. Clinical endocrinal (oxf) 1999 ; 56: 655 – 659
17. Feek CM, Sawers JS, Brown NS, et al. Influences of thyroid status on dopaminergic inhibition of thyrotropin and prolactin secretion: evidence for an additional feedback mechanism in the control of thyroid hormone secretion. J Clin endocrinol metab 1980; 51:585-589.
18. Kramer MS, Kaunchansky A, Genel M. Adolescent secondary amenorrhea: association with hypothalamic hypothyroidism. J Pediatr 1979 ;94:300-303
19. Scanlon MF, Chan V, Health M, et al. Dopaminergic control of thyrotropin alpha subunit, thyrotropin beta subunit, and prolactin in euthyroid and hypothyroidism: dissociated responses to dopamine receptor blockade with metoclopramide in hypothyroid subjects. J Clin endocrinol metab 1981 ; 53:360-365
20. Berek & Novak's Gynaecology 14th edition chapter 28 page 1101
21. Quigley ME, Judd SJ, Gilliland GB, et al. Effects of a dopamine antagonist on the release of gonadotrophin and prolactin in normal women and women with hyperprolactinemic anovulation. J Clin endocrinol metab 1979 ;48 : 718-720
22. Bohnet HG, Dahlen HG, Wuttke, et al Hyperprolactinemic anovulatory syndrome. J Clin endocrinol metab 1976; 42:132-143
23. Franks S, Murray MA, Jaquier AM et al. incidence and significance of hyperprolactinemia in women with amenorrhea. J Clin endocrinol metab (oxf) 1975; 4: 597 – 607.
24. Berek & Novak's Gynaecology 14th edition chapter 27, page 1055.