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Hormonal Diagnosis of Menstrual Irregularities or Secondary Amenorrhoea

Ursula Zollner

*Department of Obstetrics and Gynecology
University of Würzburg
Germany*

1. Introduction

In the daily clinical routine, clarification of menstrual irregularities is one of the major essentials for consultation in gynaecological practice. For an effective therapy, it is necessary to know the exact cause of the bleeding disorders. Menstrual irregularities can be the expression of a disturbed ovarian function or another disorder, usually uterine pathology. The type of menstrual irregularity is not necessarily indicative of the underlying disorder so that the examination of the levels of hormones is indispensable. Moreover, an organic cause of the bleeding disorder should be excluded. Whether the ovulatory cycle is associated with normal follicle maturation and corpus luteum function has to be clarified in the treatment of childlessness. The existence of anovulatory cycles or cycles with corpus luteum insufficiency can be normal in specific phases of life, e.g., puberty or peri-menopause. The issue of therapy should be addressed briefly. Firstly, the symptoms such as bleeding disorders and the disease patterns which are responsible for it should be highlighted. The clarification of menstrual irregularities is not only important in sterility therapy, they also influence the quality of life (1). Furthermore, hormonal disorders which are associated with chronic oestrogen or progesterone deficiency have an impact on the overall health (2). The following review represents the diagnostics of hormone-related menstrual irregularities in the fertile phase of life. The issue of bleeding disorders with the application of hormone preparations is not addressed.

2. Diagnostics of menstrual irregularities

Menstrual irregularities or bleeding disorders also include menstrual cycle-related symptoms such as dysmenorrhoea (1). During the classification of menstrual irregularities and/or bleeding disorders the only symptom which is assumed is bleeding, however, it does not contain any information about the cause of the deviation from regular menstrual cycles. A regular menstrual cycle with a 28-day bleeding interval in 85–90% of the cases is usually associated with normal ovarian function and corresponding ovulatory cycles (3). The normal bleeding duration is between 3–7 days and is associated with a blood loss of 30–40 ml (1). Deviations in the form of menstrual bleed which occur too infrequently or too frequently can be the expression of a pathological disorder. The causes can be uterine

pathology, other illnesses or ovarian dysfunction. It can be assumed that 90% of all bleeding disorders are hormone-related or partly hormone-related (4). The menstrual irregularity can express itself through a change of the bleeding pattern (menstrual rhythm abnormalities), the intensity of bleeding, its duration (type of menstrual abnormalities) or in the form of additional bleedings. The bleeding disorders are to be interpreted with the age and/or the reproductive phase of the woman, respectively. An oligomenorrhoea in a 26-year-old obese patient is most likely to be due to a PCO syndrome. However, in a 46-year-old patient it probably indicates a perimenopausal condition. The physiological and/or the therapeutic menstrual irregularities must be disassociated from the pathological menstrual irregularities, e.g., the oligomenorrhoea in the perimenopause or the amenorrhoea under gestagen monotherapy.

3. Medical history

Whilst reviewing the medical history, all previous and current diseases (disorders of the liver or kidney function, autoimmune diseases) are inquired about. The current complaints, the medication (influence of prolactin production) and the questions concerning androgen-induced disorders are just as important questions as the questions concerning contraception, desire to have children or previous pregnancies. Lifestyle (sleep, physical activity) and eating habits must not be underestimated because endocrinological problems occur frequently in both overweight and underweight women as well as in the competitive athletes. Even extreme weight fluctuations can have an impact on the ovarian function. In this conjunction, the extremely important question concerns the coagulation dysfunctions because the execution of anticoagulation can influence the bleeding duration and intensity. Furthermore, questions should be asked about the presence of endocrinopathies such as diabetes mellitus (type I), Addison disease, Cushing disease, previous operation on the uterus and or the ovaries and/or operation or trauma of the pituitary area.

4. Menstruation history

During the medical history, attention should be paid to the exact increase in bleeding intervals. The patients often view their menstrual cycle is normal even if the intervals between them do not correspond to the standard of 24 to 34 days. However, a menstruation calendar can address the intervals, duration and the intensity of the bleeding. The estimation of the bleeding intensity is strongly influenced, therefore, number of sanitary towels and/or tampons per day is advised to be recorded. If lower abdominal pain is indicated then it is important to observe the temporal relation with the periods. A dysmenorrhoea can be a sentinel for an endometriosis. Premenstrual complaints such as headaches or mood swings can be the sign of premenstrual syndrome, an indication of corpus luteum insufficiency.

5. Clinical examinations

It is important to note that an acyclic vaginal bleeding does not always need to be an expression of a disturbed ovarian function. A large number of other factors, e.g., colpitis,

ectopy, disturbed pregnancy or malignancies can become noticeable through a bleeding from the vagina and can often be diagnosed through the use of a speculum and/or a vaginal sonography. Physical and a gynaecological examination cannot be avoided during the diagnostic investigation of menstrual irregularities. The Body-Mass-Index, fat distribution pattern as well as androgen-induced disorders are very important, particularly in conjunction with the suspicion of PCO syndrome. During the gynaecological examination, infections, new formations or malformations of the internal genitals can be detected or excluded. Myomas, polyps or carcinomas should not be excluded as a cause for the bleeding. The vaginal sonography represents a substantial diagnosis test. By doing so, the condition and size of the uterus, endometrial thickness and the amount of layers as well as the form and the size of the ovaries can be assessed reliably. Follicular presence or absence is a good diagnostic criterion in assessing the egg cell reserve of the ovaries.

6. Hormonal diagnosis

Suspected diagnoses can usually be made through the type of the menstruation irregularity, symptoms and the results of the gynaecological examinations, which can then either be confirmed or excluded through a differentiated laboratory diagnosis. Therefore, an obese patient with secondary oligomenorrhoea and polycystic ovaries most likely suffers from PCO syndrome or a hyperandrogenemia. Conversely, a slim competitive athlete with a secondary amenorrhoea probably suffers from hypogonadotropic ovarian insufficiency. The menstrual phase must be taken into consideration when a blood sample is taken for investigation. It is proved to be useful to carry out the examination in the early follicle phase that is 3rd–5th days of menstruation. In secondary amenorrhoea, the question of selecting menstrual phase does not arise. The interpretation of hormones within the framework of the menstrual events implies the knowledge of the day of menstruation, the length of menstruation, the sequential secretion of the individual hormones during the course of a menstrual cycle and the relationship to one another (2, 8). The following hormones can be determined during the basic diagnostics (basic hormone analysis, [BHA], 3rd–5th days of the menstrual cycle). The following blood test should be done in a stress-free morning in early follicle phase:

- FSH (follicle-stimulating hormone)
- LH (luteinizing hormone)
- E₂ (estradiol)
- Progesterone
- Prolactin
- Testosterone
- Androstenedione
- DHEAS (dehydroepiandrosterone sulphate)
- 17-OH-Progesterone
- TSH (thyroid-stimulating hormone)

Depending on the assumed disease pattern, not all hormones need to be examined, rather it can be limited to the most relevant ones (see below). Table 1 shows the normal values of these hormones.

Hormone	Normal values
FSH	2 – 10 mIU/ml
LH	2 – 10 mIU/ml
Estradiol	25-200 pg/ml
Progesterone	< 1.0 ng/ml > 12 ng/ml in luteal hase
Prolactin	< 10 ng/ml
Testosterone	< 0.4 ng/ml
DHEAS	< 3.0 µg/ml
Androstendion	0.47-2.68 ng/ml
17-OH-Progesterone	0.2-1.0 ng/ml
TSH	0.2-3.5 µIU/ml

Table 1. Normal values of basic hormone analysis [BHA], 3rd-5th days of the menstrual cycle (3, 6)

7. Monitoring the menstrual cycle

If a largely inconspicuous menstrual rhythm is present, it is interesting in sterility diagnosis to see whether it really leads to ovulation or to a stable luteal phase. Follicle maturation disorder or corpus luteum insufficiency cannot be diagnosed through only one single blood test. Several examinations concerning the menstrual cycle are necessary. In this connection, the vaginal sonography can be implemented in addition to the laboratory diagnosis. One would expect the following values in such a diagnostic cycle:

- Day 3-5: BHA values are normal (see Table 1)
Vaginal sonography: small endometrium , ovaries with a few small preantral follicles
- Day 12-14: LH normal or ↑, estradiol > 150 pg/ml
Vaginal sonography: endometrium approx. 10 mm, mostly three-layered, dominant follicle approx. 16-20 mm
- Day 21: Progesterone > 10 ng/ml
Vaginal sonography: endometrium approx. 10 mm, homogeneous, Corpus luteum with interior echoes

In the case of deviations, conclusion about the underlying disorder can be drawn. The carrying out of LH-urine tests for the determination of ovulation period which indicates the pre-ovulatory LH surge in the spontaneous menstrual cycle is in practice (5). Both the FSH levels and FSH/LH ratio (for values > 3.6 a reduced build up of follicles must be expected) as well as the AMH (Anti-Müller hormone) are used for evaluation of the ovarian reserve.

8. Practical approaches to the individual menstrual irregularity

In 1987, Hammerstein tried to classify the bleeding disorders according to their causes (9). This is how the functional (physiological) bleedings are differentiated from dysfunctional (hormonal cause) bleedings. Furthermore, iatrogenic (contraception, HRT) systemic

(systemic diseases such as coagulation disorders) bleedings are differed from organic (carcinoma, myoma, polyp) bleedings. Our suggestion is however, to classify the bleeding disorders according to the usual patterns and then to search for their causes (7). If a hormonal disorder is responsible instead of an organic disorder, the type of ovarian disorder can be defined more precisely, e.g., oligomenorrhoea in the case of PCO syndrome (WHO II) or secondary amenorrhoea in the case of hyperprolactinaemia (WHO VI). In the case of the following suggestions with regards to the practical approach, it is essential that an organic cause for the bleeding disorder (myoma, carcinoma, infection, coagulation disorder) has been excluded.

8.1 Primary amenorrhoea

The clarification of the primary amenorrhoea is not addressed here in greater detail. What is of greater importance than hormone diagnostics is the evaluation of secondary sexual characteristics. For example, if the breasts and pubic hair of a 17-year-old patient are normal it can be assumed that she has normal ovarian functions. In most cases a diagnosis (e.g., hymenal atresia or Mayer-Rokitansky-Küster syndrome) can be made through an exact evaluation of the internal sexual characteristics. If the secondary sexual characteristics are inadequately pronounced (infantile, virilised), a large number of diseases must be considered (delayed puberty, Turner syndrome, androgen receptor defects) whose clarification should at best be carried out in a special endocrinological consultation.

8.2 Secondary amenorrhoea

If the period fails to appear for more than three months although a spontaneous menstruation took place previously, then one speaks of a secondary amenorrhoea. It goes without saying that in this situation a pregnancy must be excluded. In order to prove at which level the disorder has occurred, the provision of the following hormone analysis should be adhered to:

- FSH, LH, estradiol, testosterone, androstendione, DHEAS, prolactin and TSH

At the same time, the sonographic image of the ovaries and the endometrium is relevant. The FSH, LH and estradiol values should be correlated with the sonographic image of the internal genitalia because the levels of the individual hormone are extremely variable on phases of the menstrual cycle and in the case of amenorrhoea one does not have a reference point for the last bleeding. In the case of increased FSH, LH and estradiol values for example, a highly established three-layered endometrium is present then one should rather think of a periovulatory than a perimenopausal situation. For the further diagnostic investigation, a menstrual cycle should be waited for or initiated (2).

8.3 Oligomenorrhoea

If possible, a basic diagnosis should be carried out on the 3rd–5th days of menstruation. The diagnostic investigation is not substantially different from the clarification in the case of the secondary amenorrhoea. Due to the clinically suspected PCO syndrome, the 17-OH-progesterone should also be codetermined. If it is increased, then a late-onset AGS (androgenital syndrome) can cause the symptoms. An ACTH test and a molecular-genetic clarification, if possible, would be necessary for further diagnostics.

- FSH, LH, estradiol, testosterone, androstendione, DHEAS, prolactin, 17-OH-progesterone and TSH
- If blood sampling is not possible in early follicle phase of the menstrual cycle, in addition, progesterone should be codetermined.

8.4 Polymenorrhoea

Most of the polymenorrhoeas are an expression of corpus luteum insufficiency, which in turn is due to a follicle maturation disorder. A normal luteal phase lasts for approx. 14 days, in case of duration of 10 days, an insufficient luteal phase can be assumed. Polymenorrhoeas however, can also occur in the case of a chronic anovulation as occurs in PCO syndrome. If a perimenopausal situation is present, one can limit it to the determination of FSH, LH and estradiol, otherwise a clarification as with oligomenorrhoea should take place.

- FSH, LH, estradiol, testosterone, androstendione, DHEAS, prolactin, 17-OH-progesterone and TSH
- Determination of progesterone in the mid-luteal phase for the demonstration of a corpus luteum insufficiency

8.5 Metrorrhagia and menorrhagia

In 30% of the cases, metrorrhagias have organic causes, 70% of the causes have to do with a dysfunctional bleeding which was triggered by persistent follicles or other hormonal disorders (1). Organic causes however include infections, myomas, carcinomas or coagulation disorders. Defining a bleeding disorder in a perimenopausal situation is difficult because it is often difficult to allocate it to one menstrual cycle (7). Metrorrhagias and menorrhagias often occur in the transitional phases such as puberty or perimenopause. If the progesterone challenge remains absent despite the high estradiol concentration as with the follicle persistence, the over-proliferated endometrium is rejected. A stepwise diagnostic investigation is recommended:

- FSH, LH, estradiol
- Determination of progesterone at mid-luteal phase for the demonstration of corpus luteum insufficiency
- Possible further search for the causes through a complete BHA

8.6 Supernumerary bleeding

All forms of the bleeding are referred to as 'supernumerary bleedings' which occur cyclically and in addition to the normal menstrual bleeding. A distinction is made between premenstrual, postmenstrual or ovulatory bleeding depending on the time of its occurrence. These bleedings are also referred to as 'spitting', and its duration is less than three days. A premenstrual spotting is usually due to a relative progesterone deficiency, and a postmenstrual spotting can be indicative of a very low estradiol production. Both of these can be an expression of a follicle maturation disorder and/or the former can be due to corpus luteum insufficiency. An ovulatory bleeding can be caused by a rapid post-ovulatory estradiol deficiency. Supernumerary bleedings can also be due to organic causes such as polyps, myomas, carcinomas, infections or coagulation disorders. If there is no desire to have children and if there is no strong indication of an

endocrinopathy, a diagnostic investigation in the form of hormone analysis is not essential because a symptomatic therapy with a hormone preparation usually leads to the satisfaction of the patient.

8.7 Type of menstrual abnormalities

In the case of the differential diagnosis clarification of hypomenorrhoeas or hypermenorrhoea, it should be noted that heavier bleeding is often triggered by a uterus myomatosus or a long-term anticoagulation. If an organic and/or systemic cause is excluded, a symptomatic therapy is preferred. As a general rule, a hormone analysis is not necessary, except when there is the desire to have children.

9. Differentiation of ovarian dysfunctions

Menstrual irregularities (deviations from the regular four-week bleeding intervals) are usually accompanied by an ovulatory disorder so that one cannot consider the entities, menstrual irregularities and ovulatory disorders separately. The bleeding disorder is the external sign that a possible disturbed ovarian function is present. The definition is purely descriptive (7). However, as has already been mentioned, other factors can be responsible for the deviation from normal menstrual cycle, e.g., infections or uterine causes. Uterine factors, such as myomas, are in turn favoured by hormonal imbalances so that here the transitions are fluent. If a disturbed ovarian function is present, an exact diagnosis could be made through laboratory determination of most of the important hormones. According to WHO, ovarian insufficiencies are classified in seven groups (7). To be specific, it relates to a classification of the amenorrhoeas. The individual endocrine disease pattern can also be reflected in menstrual rhythm abnormalities, such as oligomenorrhoeas or polymenorrhoeas. The exact knowledge of at what level the disorder is present is indispensable in order to be able to initiate an effective therapy.

10. Hypogonadotropic ovarian dysfunction

Hypogonadotropic amenorrhoea is usually functional (WHO Group I), with organic causes (Group VII) such as tumours or traumas are rare. A disturbed pulsatility of the GnRH secretion can lead to an insufficient FSH and LH production and consequently results in follicle maturation disorder. The causes for the functional disorder are extreme stress situations, such as anorexia nervosa, famines (war amenorrhoea) or intense physical exercise, such as competitive sports. An amenorrhoea is usually present but oligomenorrhoea is also possible.

10.1 Diagnostics

- Estimation of FSH, LH, estradiol, progesterone, prolactin, testosterone, androstendione, DHEAS and TSH:
 - Decreased gonadotropines, estradiol is also low.
 - A low level of progesterone points to a pre-ovulatory or ovarian dormancy.
 - To exclude hyperprolactinaemia and/or hyperandrogenaemia, determination of androgens and of prolactin should be considered.

- TSH levels to exclude altered thyroid gland function.
- Due to suspected organic causes (additional symptoms such as headaches, impaired vision or dizziness and/or no functional cause for the hypogonadotropic situation) a MRT examination should be carried out.
- A GnRH test can be carried out in order to eliminate the possible hypothalamic or pituitary causes (3).

10.2 Therapy

In case of organic causes if necessary, an operation is indicated. In case of functional disorders, a causal treatment such as weight gain in the case of anorexia should be strived for if possible. In addition, in case of low estradiol levels, HRT should be indicated and if there is a desire to have children, hormonal stimulation should be indicated if necessary.

11. Hypergonadotropic ovarian dysfunction

WHO Group III represents the hypergonadotropic ovarian insufficiencies. If secondary oligomenorrhoea or amenorrhoea is present then (physiological) perimenopausal situation and/or premature failure of the ovarian function (age > 40) can be thought of (increased FSH and LH levels).

11.1 Diagnostics

- Determination of FSH, LH, estradiol, progesterone, prolactin, testosterone, androstendione, DHEAS and TSH:
 - FSH and/or LH are elevated, estradiol low
 - A low level of progesterone indicates a pre-ovulatory or ovarian dormancy
 - To exclude hyperprolactinaemia and/or hyperandrogenaemia as well as dysfunction of the thyroid gland, determination of androgens, prolactin and TSH is essential.
- Due to suspected POF, further diagnostic investigations (e.g., chromosome analysis to exclude Turner syndrome, search of autoimmune diseases or associated endocrinopathies) are essential.

11.2 Therapy

In case of young patients, there is an indication for hormone replacement therapy in order to avoid oestrogen-deficient situations. If there is a desire to have children, a hormonal stimulation with FSH can be tried depending on the starting situation, however, with little prospect for success.

12. Hyperprolactinaemia

Hyperprolactinaemic ovarian dysfunctions can be due to many causes. If the disorder is pronounced, an amenorrhoea can be present, in most cases however, there are menstrual irregularities such as oligomenorrhoeas or anovulatory eumenorrhoeas. If there is an ovarian insufficiency caused by prolactinoma it must be allocated to WHO Group V. The amenorrhoeas which are caused by drugs or other hyperprolactinaemic amenorrhoeas are allocated to WHO Group VI. Increased prolactin levels lead to an ovarian dysfunction

through a disturbed GnRH pulsatility but also through an influence on the adrenal cortex in terms of inducing adrenocortical hyperandrogenaemia.

12.1 Diagnostics

- Determination of FSH, LH, estradiol, progesterone, prolactin, testosterone, androstendione, DHEAS and TSH:
 - Gonadotropins and estradiol are usually normal or decreased
 - Prolactin is increased, in case of values > 50 ng/ml an image diagnosis should be included.
 - An associated hyperandrogenaemia can occur
- Hypothyroidisms can lead to a hyperprolactinaemia through an increased release of TRH.
- To measure a latent hyperprolactinaemia (normal basic prolactin values) provocation tests such as metoclopramide test can be carried out.

12.2 Therapy

If possible, a causal therapy (changeover of medication) should be strived for, however, the treatment with dopamine agonists is indicated in most cases.

13. Hyperandrogenaemic ovarian dysfunction

The most common form of hyperandrogenaemic ovarian dysfunction (WHO Group II) is represented by the PCO syndrome. Ovarian insufficiencies of WHO Group II include all disorders with normal FSH levels where the interplay of gonadotropins or other factors of the central ovarian regulation (with the exception of hyperprolactinaemia) is disturbed. One main part of this group creates the hyperandrogenaemic disorders (2). The PCO syndrome is not a disease per se, rather a complex comprised of several symptoms. According to the Rotterdam classification from 2003, two of the three criteria must be present so that the PCOS diagnosis can be made (10):

- Oligoovulation or anovulation
- Clinical and/or biochemical sign of hyperandrogenisation
- Polycystic ovaries and the exclusion of other causes (congenital adrenal hyperplasia, androgen producing tumours, Cushing disease).

In case of PCOS, different causes can lead to a similar disease pattern. The most common menstrual irregularity in case of PCO syndrome is represented by oligomenorrhoea. In case of insufficient follicle maturation, an amenorrhoea can also be present. Even polymenorrhoea is possible through follicular disorder without ovulation or with consecutive corpus luteum insufficiency.

13.1 Diagnostics

- Determination of FSH, LH, estradiol, progesterone, prolactin, testosterone, androstendione, DHEAS, 17-OH-progesterone and TSH:
 - LH/FSH > 1.5-2
 - Estradiol can be normal, decreased or even elevated
 - Hyperandrogenaemia, depending on the individual androgens, can be differentiated with the knowledge of their production areas (ovarian and adrenal hyperandrogenaemia).

- An ACTH test to exclude late onset AGS should take place if there is an increase of 17-OH-progesterone. A molecular genetic inspection can be carried out in the case of a striking ACTH test. The heterozygous form of 21 hydroxylase deficiency (most common cause for late-onset AGS) often remains latent during childhood. It manifests itself in women usually after puberty in the form of menstruation irregularities, androgenisation appearance or a PCO syndrome.

13.2 Therapy

Depending on the cause, living situation and symptoms, an antiandrogen ovulation inhibitor, ovarian stimulation with clomiphene, low dose FSH or corticosteroid treatment comes into question.

14. Corpus luteum insufficiency

Corpus luteum insufficiency relates to the normogonadotropic ovarian dysfunction. The cause for this is usually a follicle maturation disorder in the first half of the menstrual cycle which can lead to an insufficient formation of the corpus luteum. The luteal phase is shortened to less than 10 days so that it leads to a shortening of the cycle. Often premenstrual spotting is evident. The progesterone levels are too low. In the perimenopause phase, similar situation appears (physiological). However, the development of myomas or an endometriumperplasia, which in turn can aggravate the bleeding disorder, can be favoured through the relative progesterone deficiency. Corpus luteum insufficiency can be concomitant of other endocrine disorders. In case of a desire to have children, the cause should be carefully searched for.

14.1 Diagnostics

- Determination of progesterone in the mid-luteal phase (repeated > 10 ng/ml)
- For differential diagnosis BHA with FSH, LH, estradiol, prolactin, testosterone, androstendione, DHEAS and TSH are to be carried out:
 - FSH, LH and estradiol within the normal range
 - The determination of androgens, prolactin and TSH to be made to exclude hyperprolactinaemia and/or hyperandrogenaemia as well as dysfunction of the thyroid gland.
- If basal body temperature is managed (> 10 days of luteal phase).

14.2 Therapy

When planning to have children, an ovarian stimulation therapy can lead to an improved follicle maturation and more efficient formation of the corpus luteum.

15. Dysfunctions of the thyroid gland

Dysfunctions of the thyroid gland can lead to menstrual irregularities through the influence of the hypothalamic-pituitary system (WHO Group II). Hypothyroidism in particular is very important for gynaecological endocrinology. Clinical symptoms such as cold intolerance, reduced performance or dry, cold skin may confirm the diagnosis of

hypothyroidism. Hyperthyroidism can become noticeable through heat intolerance, moist and warm skin or tachycardias. Menstrual irregularities can occur in both the circumstances.

15.1 Diagnostics

- Determination of FSH, LH, estradiol, progesterone, prolactin, testosterone, androstendione, DHEAS and TSH:
 - Hypothyroidism: TSH increased, hyperthyroidism: TSH decreased
 - Gonadotropins can be normal or depleted
 - Hyperprolactinaemia possible
 - Hyperandrogenaemia possible
- A TRH test should be carried out.

15.2 Therapy

If a dysfunction of the thyroid gland is diagnosed, dysfunction-related treatment should be installed and continued. In case of good thyroid function, repeated basal hormonal analysis is recommended.

16. Conclusion for the practice

Menstrual irregularities are usually contingent on ovarian dysfunction. The level of disorder can be identified after excluding organic causes through a basal hormonal analysis and thus an adequate therapy can be introduced. This chapter describes which hormones should be evaluated (11).

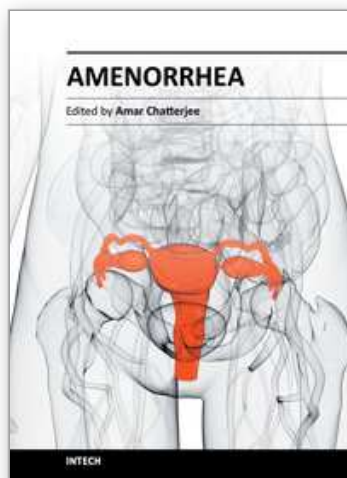
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This book on "Amenorrhea" is a wonderful collection of updated reviews dealing mostly with the aphysiological aspects of secondary amenorrhea. The book represents a collection of eight chapters, each chapter in the book is written by the international experts with extensive experience in the areas covered. We hope that readers will find this book interesting, helpful and inspiring.

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