Kallmann's Syndrome: A Rational Approach to Diagnosis

Mary Eleanor B. Domingo; Ma. Asuncion A. Fernandez, MD and Maria Isadora Margarita Yap-Garcia, MD
Section of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, St. Luke's Medical Center, Quezon City

Kallmann's syndrome is a rare neuronal migration disorder characterized by hypogonadotropic hypogonadism and anosmia or hyposmia. This case details a 30 year-old female who presented with primary amenorrhea, delayed pubertal development and hyposmia. Clinical parameters and hormonal assays were consistent with hypogonadotropic hypogonadism. Transvaginal sonography revealed infantile uterus and small ovaries. Magnetic resonance imaging (MRI) of the brain validated our diagnosis revealing aplasia of bilateral olfactory bulbs and shallow olfactory sulci. Hormonal replacement therapy has been instituted to promote breast development and avoid the detrimental effects of estrogen deficiency. A thorough evaluation to identify possible co-existing anomalies is in progress. This paper highlights an algorithm that effectively utilizes modalities available in our setting to establish diagnosis in patients presenting with primary amenorrhea.

Key words: Kallmann's syndrome, hypogonadotropic hypogonadism, primary amenorrhea, hyposmia

Introduction

The clinical assessment of amenorrhea can be a diagnostic challenge due to its complex and varied etiologies. Diagnostic possibilities can have serious consequences if not recognized and treated effectively. However, when approached logically and systematically, evaluation can be straightforward.

Kallmann's syndrome is an inherited disorder characterized by hypogonadotropic hypogonadism and hyposmia or anosmia.[1-4] Initially reported by Aureliano Maestre de San Juan in 1856[5,6] and later identified as a clinical entity by Franz Josef Kallmann in 1944,[1] it is seldom encountered clinically with an incidence of 1:10,000 in males and 1:50,000 in females.[7,8] Kallmann's syndrome is an anomaly of neuronal migration wherein cells that differentiate into gonadotropin releasing hormone (GnRH) fail to migrate along fascicles of vomeronasal and terminalis nerves into the forebrain.[9,10] This arrest in migration results in different degrees of luteinizing hormone (LH) and follicle stimulating hormone (FSH) deficiencies leading to amenorrhea, clinical evidence of hypogonadism and incomplete maturation of secondary sexual characteristics.[9,10] Abnormal development of olfactory placode results in improper development of olfactory bulbs and sulci leading to anosmia or hyposmia.[10]

Despite the classical features of Kallmann's syndrome, its diagnosis can be easily overlooked if not appropriately investigated. Furthermore, the presence of associated developmental anomalies should be scrutinized. This case will highlight systematic deduction of a patient with primary amenorrhea, delayed puberty and hyposmia to establish a rare diagnosis.

The Case

A 30 year-old female was referred to our section due to primary amenorrhea, delayed pubertal development and hyposmia.

At age 19, she was 4 feet (121 cm) tall, weighed 30 kg and had not developed secondary sexual characteristics such as breast budding or pubic hair. At age 20, she noted gradual increase in body weight followed by growth spurt until she reached her present height (154 cm). Breast and pubic hair development were, likewise, noted but eventually ceased to progress.

Due to financial constraints, no medical consultation was done until age 29 when she was seen by a gynecologist for amenorrhea. A transvaginal ultrasound was done revealing an infantile uterus, atrophic endometrium and non-visualized ovaries. She was referred to a reproductive endocrinologist and physical examination at this time revealed Tanner stage 3 breast and pubic hair development and infantile genitalia. Hormonal evaluation was performed revealing low serum FSH and normal estradiol, prolactin and TSH levels (Table 1). Karyotype determination was done revealing 46,XX (Figure 1). Financial constraints precluded magnetic resonance imaging (MRI) of the brain. Patient was treated as a case of hypogonadotropic-hypogonadism, probably Kallmann's syndrome. She was started on Estradiol (Progynova) 1 mg OD. Breast enlargement and monthly withdrawal bleeding were noted, 8 days in duration, consuming 3 pads per day with associated dysmenorrhea. Medication was discontinued after 6 months of treatment due to inadequate finances. She was, again, amenorrheic after cessation of medical therapy. She was subsequently referred to our institution.

Table 1. Results of hormonal assay.

Hormonal assay	Patient's values	Normal values[10]
Serum FSH	1.27 mIU/ml	5-20 mIU/ml
Serum LH	0.30 mIU/ml	5-20 mIU/ml
Serum estradiol	79.29 pg/ml	>40 pg/ml
TSH	3.01 μIU/ml	0.45-4.5 μIU/ml
Prolactin	3.80 ng/ml	<20 ng/ml

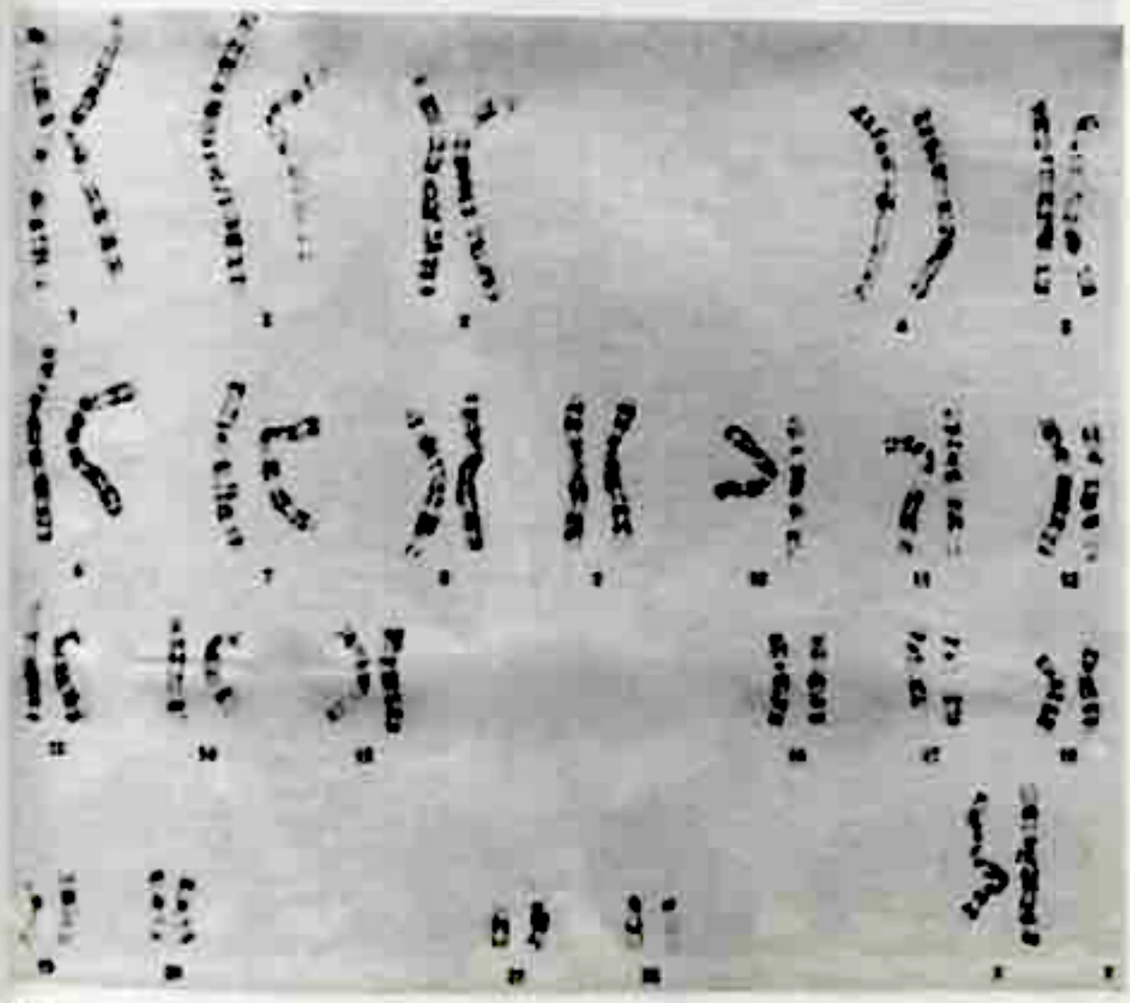

Figure 1. Karyotype 46, XX.

Patient has no history of hypertension, diabetes, asthma, thyroid problems, galactorrhea or cancer. She had no previous surgery, chemotherapy or radiotherapy. She is the 6th child of 6 siblings and the tallest in her family. All other members have height range of 149-152 cm. No other sibling exhibited delay in pubertal development. She has a family history of hypertension on her maternal side. She has no family history of birth defects, mental retardation, infertility or early menopause. She is a college graduate (computer programming) and currently works as a maid.

Menarche was noted at 29 years old after instituting estradiol treatment. Prior to treatment, she had no history of cyclic pelvic pain, hypogastric or introital masses. Sexual debut was at 26 years of age with dyspareunia. Subsequent episodes of sexual contact had episodes of dyspareunia and minimal vaginal bleeding. She had two monogamous sexual partners. No contraceptives were used. She had no previous pregnancy, history of abnormal vaginal discharges or sexually transmitted diseases.

She is a non-smoker, with occasional intake of alcoholic beverages. She has no history of substance abuse.

Review of system revealed presence of hyposmia since childhood. She had no weight loss, anorexia, vasomotor symptoms, visual or hearing disturbances, galactorrhea, bowel or urinary complaints. Her height and weight are 154 cm and 55 kg, respectively. Body mass index is within normal[11] (23.2 kg/m^2). Vital signs are stable. Nasal septum is midline, turbinates complete with pinkish mucosa and minimal discharge, (+) anosmia, bilateral nares. No high-arched palate, webbed neck, anterior neck masses or signs of hirsutism noted. Breasts (Figure 2) are symmetrical, Tanner stage 4, with no masses or nipple discharges. Waist circumference is 86 cm. External genitalia (Figure 3) is normal, Tanner 4 pubic hair development. On speculum exam (Figure 4), the cervix is smooth, closed with viscid mucus on external os. Pelvic exam revealed: 1) firm, closed cervix, 2) retroverted, small uterus and 3) no adnexal mass. Extremities were unremarkable with normal arm span (155 cm). Neurologic exam was essentially normal, apart for bilateral anosmia.

Our working impression was primary amenorrhea secondary to hypogonadotropic hypogonadism, to consider Kallmann's syndrome. Transvaginal sonography (Figure 5) revealed a small retroverted uterus measuring 2.6 cm x 2.8 cm x 2.1 cm with thin endometrium (0.20 cm) and small ovaries (right ovary 1.2 cm x 0.9 cm x 0.8 cm and left ovary 1.3 cm x 0.8 cm x 0.5 cm). Serum LH values were low (0.30 mIU/ml). Magnetic resonance imaging (MRI) of the brain was done revealing normal pituitary gland, absence of bilateral olfactory bulbs and shallow

bilateral olfactory sulci (Figure 6). Audiometric evaluation was conducted revealing normal results. Subsequent plans of the management include: 1) ultrasound of the kidneys, ureter and urinary bladder to identify urologic anomalies, and 2) Bone mineral density assessment through central dual energy x-ray absorptiometry (DEXA). Patient is currently on estradiol (Progynova) 1 mg OD for 6 months to maximize breast development, followed by combined estrogen-progesterone treatment.

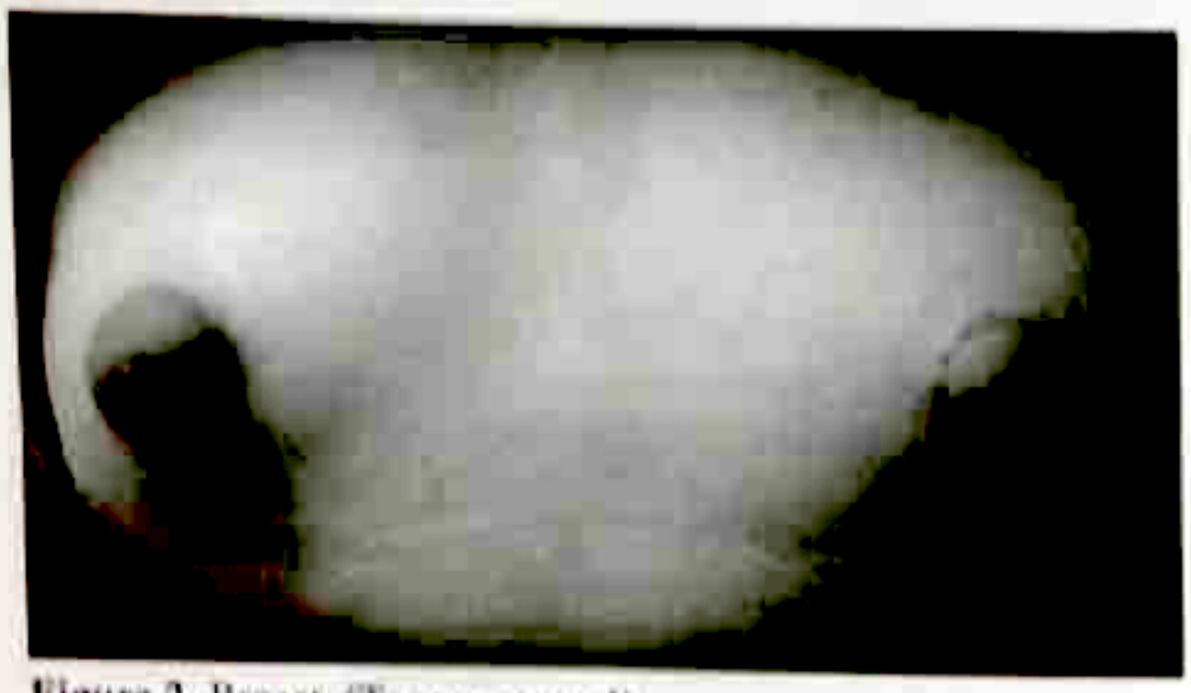

Figure 2. Breast (Tanner stage 4).

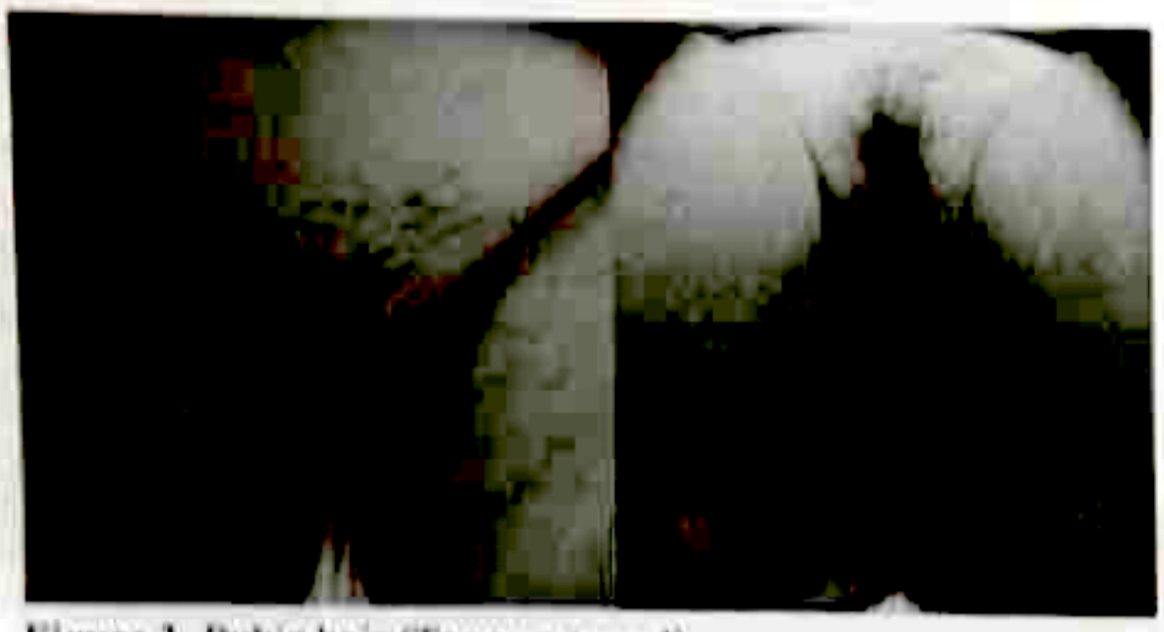

Figure 3. Pubic hair (Tanner stage 4).

Figure 4. Speculum exam.

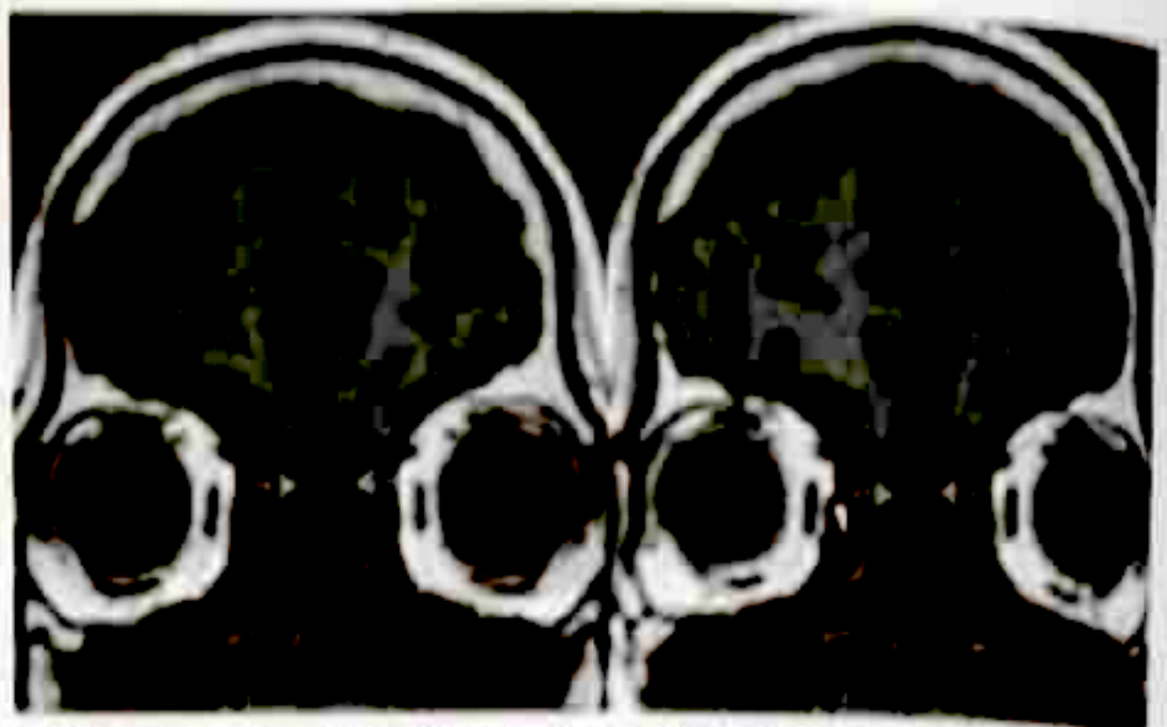

Figure 5a. Coronal T1-weighted images of our patient demonstrating absent olfactory bulbs (arrow).

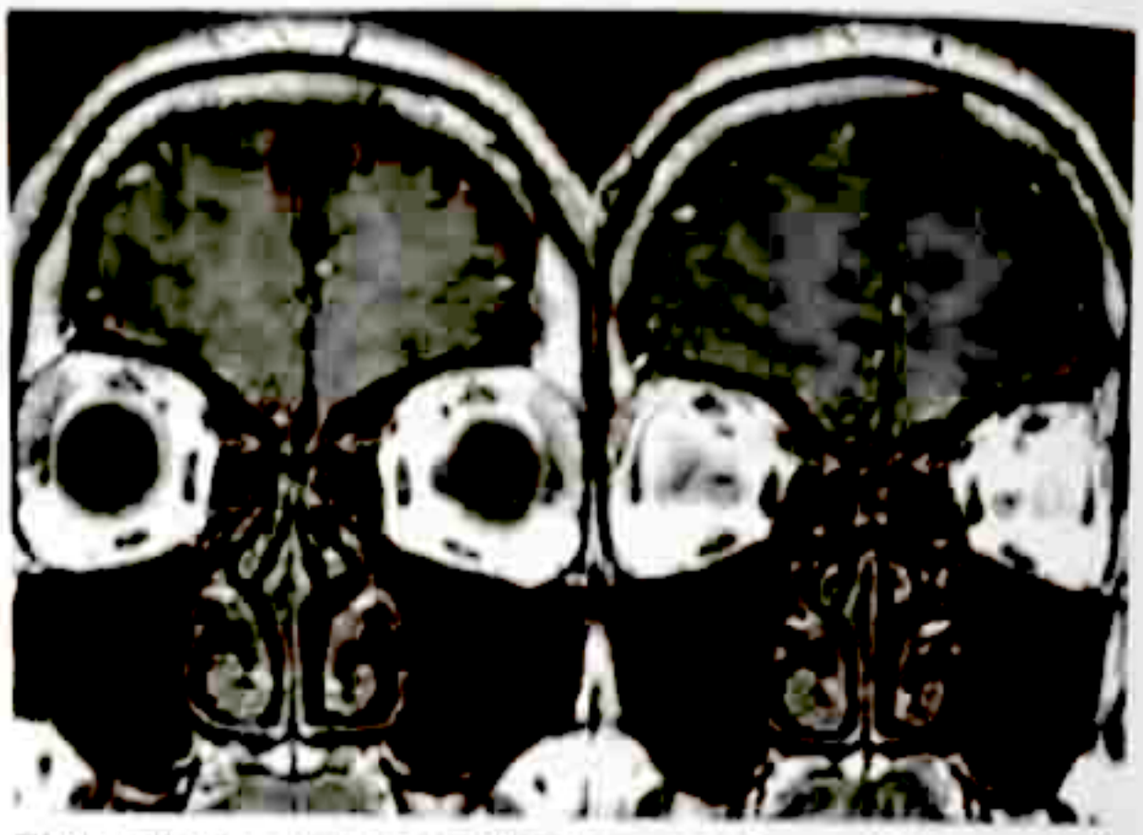

Figure 5b. Coronal T1-weighted images of normal olfactory bulbs (arrow).

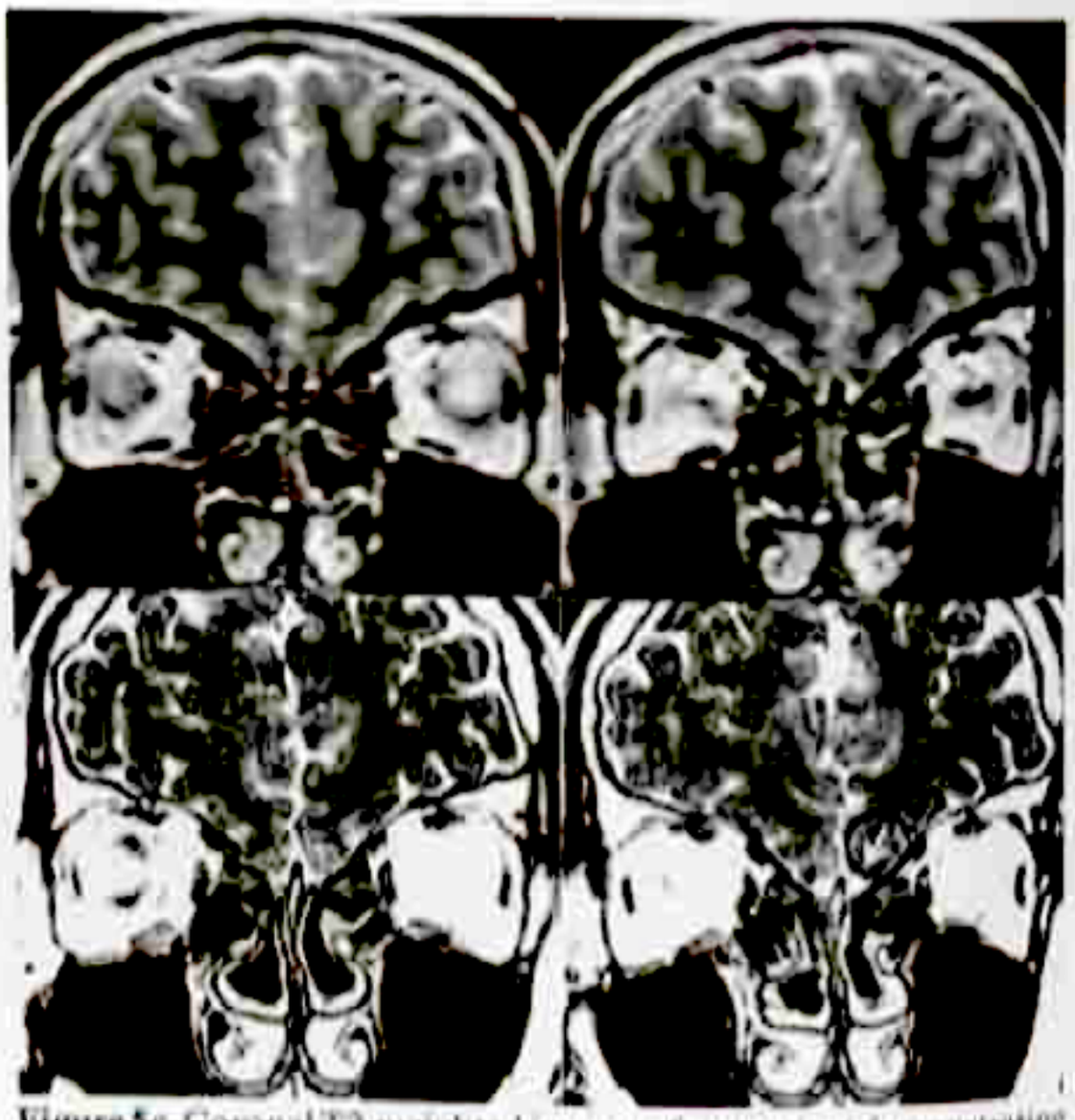

Figure 5c. Coronal T2-weighted images of our patient demonstrating absent olfactory bulbs (arrow) and shallow olfactory sulci (encircled arrow).

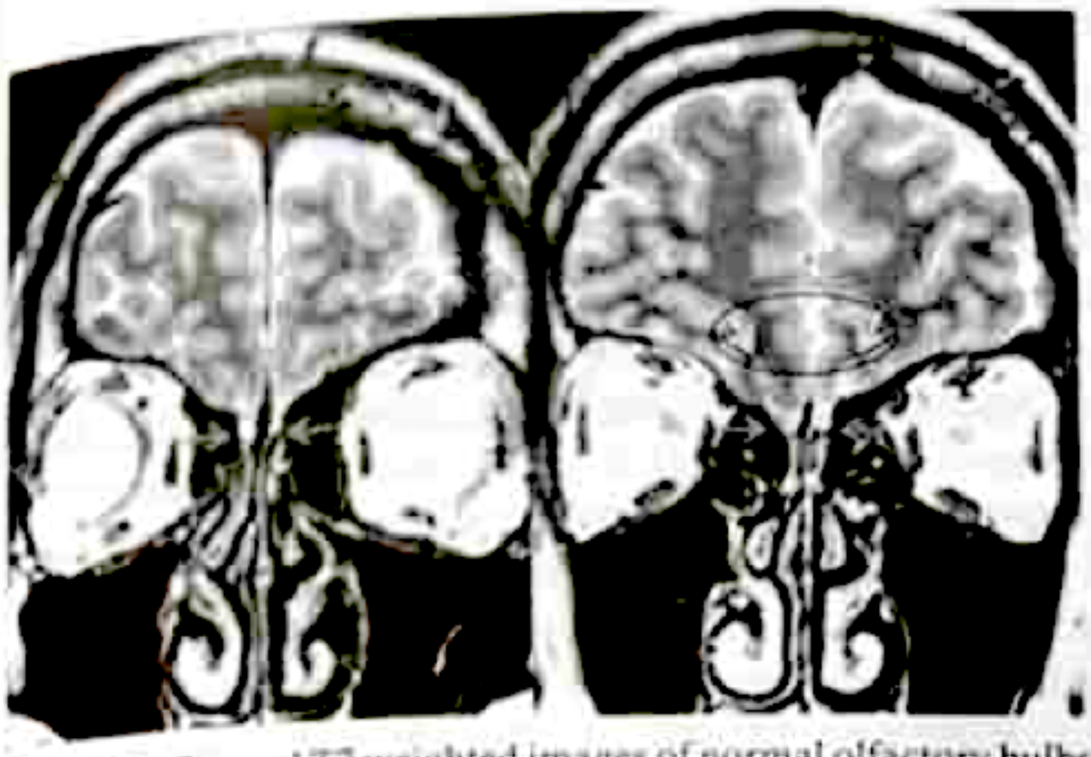

Figure 5d. Coronal T2 weighted images of normal olfactory bulbs (arrows) and olfactory sulci (encircled arrows).

Figure 5. Magnetic resonance imaging (MRI) of our patient vs. normal olfactory tract

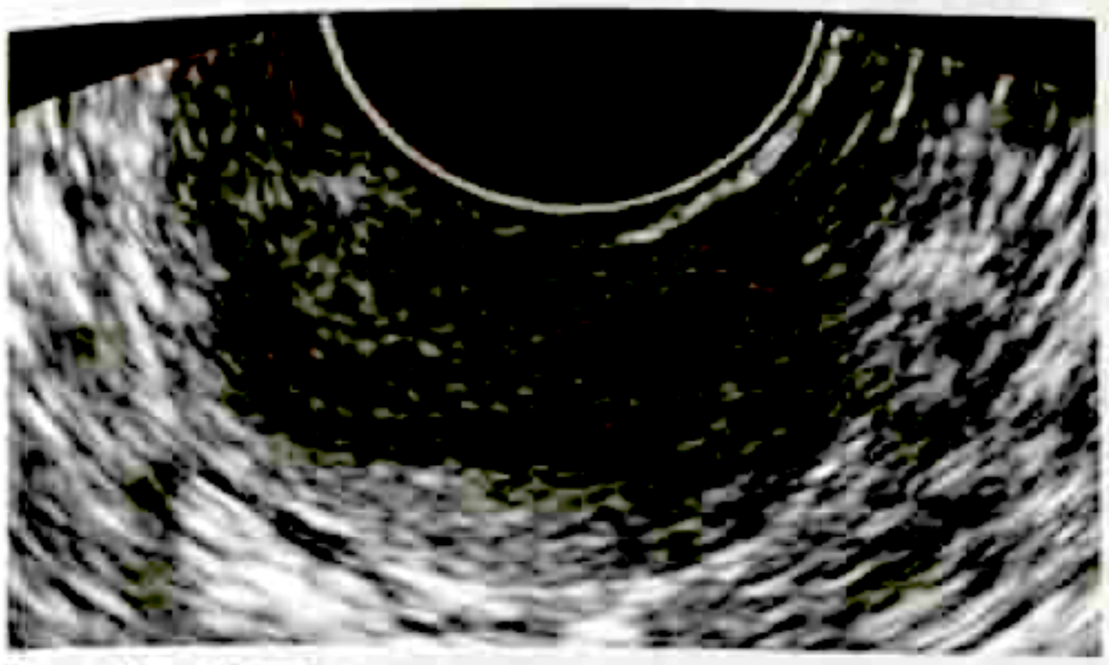

Figure 6a. Uterus.

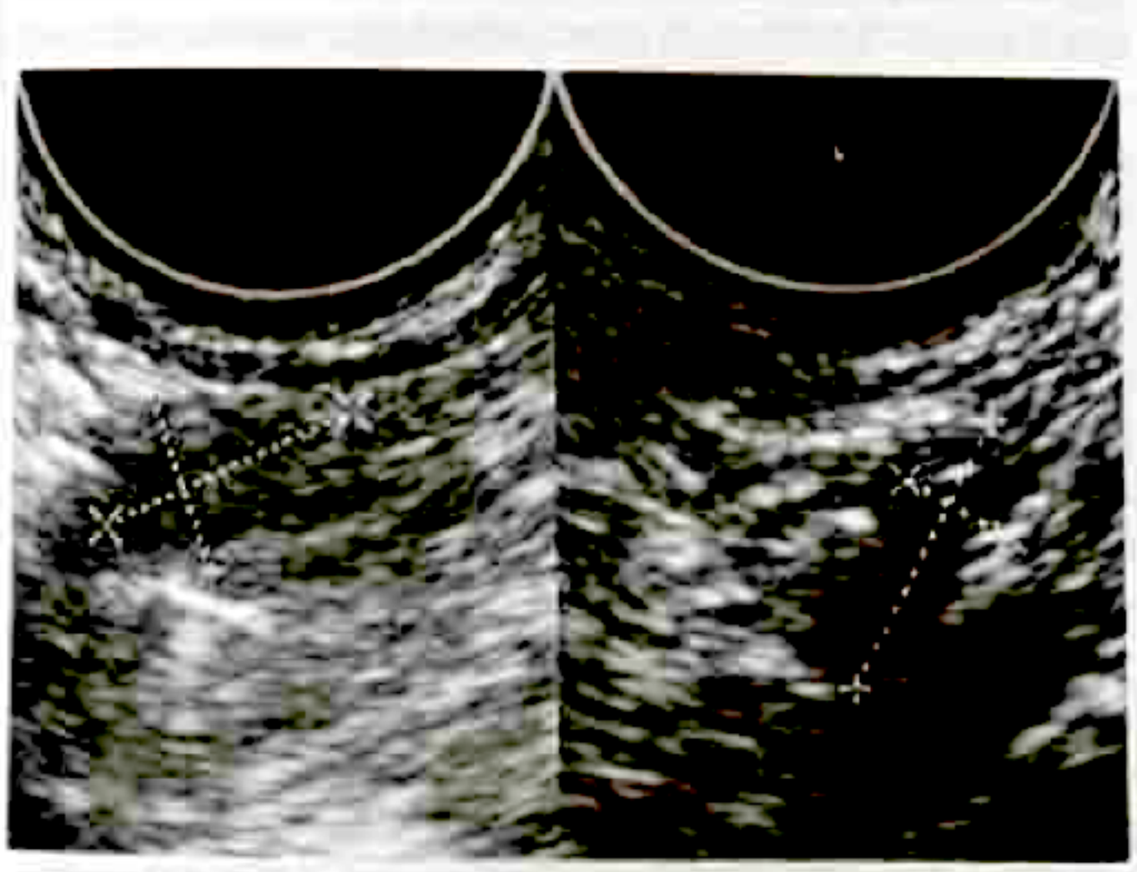

Figure 6b. Right and left ovaries.

Figure 6. Transvaginal sonography

Discussion

Menarche is a critical biomarker in the reproductive life of females.[12,13] Its average age of onset for varied populations worldwide range from 11.2 to 13.5 years old.[10] Recent studies of Filipino women revealed an average age of menarche at 12.8-13.8 years.[14,15] Thus, women fulfilling any of the following criteria should be evaluated:[10] 1) no menses by age 14 in the absence of growth or development of secondary sexual characteristics, 2) no menses by age 16 regardless of the presence of normal growth and development of secondary sexual characteristics, and 3) women who have menstruated previously, however, no menses for an interval of time equivalent to a total of at least three previous cycles or 6 months.

The evaluation of amenorrhea requires a rational and efficient approach, particularly in low-resource settings, such as the Philippines. Diagnosis has traditionally been categorized into primary and secondary amenorrhea. However, this approach serves little practical purpose and can even be misleading due to similar etiologies.[10,16] Assessment should include four anatomically and functionally distinct structural components that provide a natural and useful hierarchy for diagnosis:[10] 1) genital outflow tract and uterus, 2) ovary, 3) pituitary and 4) hypothalamus or central nervous system. Evaluation is geared towards determining the functional integrity of each compartment, beginning at the lowest level and progressing systematically to the higher levels of the system until the cause is determined.

The genital outflow tract of our patient, although underdeveloped, is essentially complete. Previous history of sexual contact, albeit with episodes of dyspareunia, implies an adequate vaginal canal. Furthermore, the presence of withdrawal bleeding after starting oral estradiol infers a patent outflow tract. Absence of previous uterine surgery or manipulation excludes iatrogenic causes of outflow tract disorders. Visualization of the cervix on speculum exam and pelvic examination revealing a small cervix and uterus further eliminates outflow tract disorders. Physical examination findings were further substantiated by transvaginal sonography.

Breast and pubic hair development are vital markers of estrogen and androgen production and exposure. Thelarche and pubarche are closely linked and progress in parallel.[10] Similar changes were observed in our patient. In contrast, the presence of asymmetrical advanced breast development with absent or scant pubic hair growth is a classical sign of androgen insensitivity syndrome (AIS) or testicular feminization.

The next level of evaluation is focused on ovarian function. Abnormalities of ovarian function are the most

common overall cause of amenorrhea and include a wide variety of disorders from chronic anovulation (PCOS, obesity, thyroid disorders and hyperprolactinemia) to complete ovarian failure. The most obvious measure of ovarian function is estrogen production.[4] Unfortunately, symptoms and signs of estrogen deficiency such as genitourinary atrophy develop gradually and are not commonly observed in young women. Vasomotor symptoms typically are absent in women with hypothalamic dysfunction. Breast development is a reliable indicator of estrogen production or exposure to exogenous estrogens.[4] During her early 20's our patient noted breast development to Tanner 3, preceded by weight gain and height acceleration. Pubertal changes, however, ceased to progress to full maturity (Tanner 5). Advancement of breast development was again noted during intake of oral estradiol, however, halting at Tanner 4 upon discontinuation of medication. Accordingly, estrogen production was initially sufficient, however was transient and eventually inadequate.

Clinically, serum estradiol levels are easy to obtain, relatively inexpensive and objective, however levels can fluctuate erratically and, therefore, can be misleading.[3,10] A random estradiol concentration greater than 40 pg/ mL indicates the presence of functional ovarian follicles.[10] Our patient's estradiol levels are, thus, within normal (79.29 pg/ ml), however, are not in conformity with her clinical features and presentation, which are more consistent with hypogonadism. Such results may reflect peripheral sources of estrogen, taking to account that our patient's BMI, although normal by international standards,[17] has been heralded as overweight for Asians based on the World Health Organization (WHO) Asia-Pacific Region 2000 guidelines on obesity.[18] Her waist circumference (86 cm) is, likewise, greater than 80 cm cut-off value for Asians[18] reflective of adiposity. In addition, normal estradiol levels can be noted during premature or normal perimenopause and occur sporadically in women with hypothalamic amenorrhea. Other methods for assessing the level of ovarian estrogen production include clinical character of cervical mucus, progestin challenge test and endometrial thickness by transvaginal ultrasonography.[10] Physical examination of our patient's genital tract revealed minimal viscid cervical mucus within the external os in contrast to clear, watery, abundant cervical mucus indicative of estrogen action. Transvaginal sonography of our patient denoted a thin endometrium (0.20 cm), reflecting substantially low level of estrogen production. Overall, the duration of amenorrhea and other clinical history and features are more important and useful for assessing ovarian function.

The serum FSH concentration is an indirect measure of ovarian function. The normal feedback relationship between ovarian estrogen production and pituitary gonadotropin secretion dictates that low estrogen levels should cause a compensatory increase in FSH release to stimulate ovarian follicular development and estrogen secretion. Thus, normal or low serum FSH level indicates the presence of functional ovarian follicles, while an elevated serum FSH concentration is a reliable indication of ovarian follicular depletion or failure.[3,10] The FSH assay of our patient (1.27 mIU/ml) is consistent with a hypergonadotropic state (<5 mIU/ml) occurring in a background of hypogonadic milieu. Low levels of gonadotropins and hypogonadism herald abnormal pituitary function or hypothalamic amenorrhea.[3,10]

Common causes of chronic anovulation and amenorrhea such as hyperprolactinemia and thyroid disorders should, likewise, be excluded.[10,19] Serum prolactin and TSH can be measured with serum FSH and estradiol at the outset of evaluation to facilitate efficiency in diagnosis. Serum prolactin and TSH values of our patient are within normal.

Having clearly deduced the hypogonadotropic hypogonadic state of our patient, we can now proceed with investigation for pituitary and hypothalamic disorders. When there is no clear explanation for hypogonadotropic hypogonadism such as significant physical, nutritional or emotional stress, imaging is indicated to exclude tumors and to help distinguish between pituitary and hypothalamic causes. Magnetic resonance imaging (MRI) with gadolinium contrast is the method of choice due to its sensitivity and accuracy for detection of abnormalities within and near the sella turcica.[10]

A distinct clinical feature of our patient, which clinches diagnosis, is the history of hyposmia. Isolated hypogonadotropic hypogonadism with associated hyposmia or anosmia is characteristic of Kallmann syndrome.[1,2,4] Although most of the Kallmann's syndrome cases are sporadic, three modes of inheritance have been reported: X chromosome-linked (KAL1), autosomal dominant (KAL2) and autosomal recessive (KAL3).[4] The classical X-linked form of the disorder is caused by a variety of genetic mutations in the KAL gene (located on the short arm of the X chromosome, Xp22.3) encoding anosmin-1, a neural adhesion molecule that promotes migration of GnRH neurons and olfactory neurons from the olfactory placode to the hypothalamus during embryonic development.[20]

The features of Kallmann's syndrome can be categorized as reproductive and non-reproductive. The reproductive features for females include delayed puberty and primary amenorrhea, noted in our patient, as well as poorly defined secondary sexual characteristics and infertility. Primary amenorrhea occurs in approximately 90% of cases of idiopathic

common overall cause of amenorrhea and include a wide variety of disorders from chronic anovulation (PCOS, obesity, thyroid disorders and hyperprolactinemia) to complete ovarian failure. The most obvious measure of ovarian function is estrogen production.[10] Unfortunately, symptoms and signs of estrogen deficiency such as genitourinary atrophy develop gradually and are not commonly observed in young women. Vasomotor symptoms typically are absent in women with hypothalamic dysfunction. Breast development is a reliable indicator of estrogen production or exposure to exogenous estrogens.[10] During her early 20's our patient noted breast development to Tanner 3, preceded by weight gain and height acceleration. Pubertal changes, however, ceased to progress to full maturity (Tanner 5). Advancement of breast development was again noted during intake of oral estradiol, however, halting at Tanner 4 upon discontinuation of medication. Accordingly, estrogen production was initially sufficient, however was transient and eventually inadequate.

Clinically, serum estradiol levels are easy to obtain, relatively inexpensive and objective, however levels can fluctuate erratically and, therefore, can be misleading.[10,16] A random estradiol concentration greater than 40 pg/mL indicates the presence of functional ovarian follicles.[10] Our patient's estradiol levels are, thus, within normal (79.29 pg/ml), however, are not in conformity with her clinical features and presentation, which are more consistent with hypogonadism. Such results may reflect peripheral sources of estrogen, taking to account that our patient's BMI, although normal by international standards,[17] has been heralded as overweight for Asians based on the World Health Organization (WHO) Asia-Pacific Region 2001 guidelines on obesity.[18] Her waist circumference (86 cm) is, likewise, greater than 80 cm cut-off value for Asians[18] reflective of adiposity. In addition, normal estradiol levels can be noted during premature or normal perimenopause and occur sporadically in women with hypothalamic amenorrhea. Other methods for assessing the level of ovarian estrogen production include clinical character of cervical mucus, progestin challenge test and endometrial thickness by transvaginal ultrasonography.[10] Physical examination of our patient's genital tract revealed minimal viscid cervical mucus within the external os in contrast to clear, watery, abundant cervical mucus indicative of estrogen action. Transvaginal sonography of our patient denoted a thin endometrium (0.20 cm), reflecting substantially low level of estrogen production. Overall, the duration of amenorrhea and other clinical history and features are more important and useful for assessing ovarian function.

The serum FSH concentration is an indirect measure of ovarian function. The normal feedback relationship between ovarian estrogen production and pituitary gonadotropin secretion dictates that low estrogen levels should cause a compensatory increase in FSH release to stimulate ovarian follicular development and estrogen secretion. Thus, normal or low serum FSH level indicates the presence of functional ovarian follicles, while an elevated serum FSH concentration is a reliable indication of ovarian follicular depletion or failure.[10,16] The FSH assay of our patient (1.27 mIU/ml) is consistent with a hypogonadotropic state (<5 mIU/ml) occurring in a background of hypogonadic milieu. Low levels of gonadotropins and hypogonadism herald abnormal pituitary function or hypothalamic amenorrhea.[10,16]

Common causes of chronic anovulation and amenorrhea such as hyperprolactinemia and thyroid disorders should, likewise, be excluded.[10,16] Serum prolactin and TSH can be measured with serum FSH and estradiol at the outset of evaluation to facilitate efficiency in diagnosis. Serum prolactin and TSH values of our patient are within normal.

Having clearly deduced the hypogonadotropic hypogonadic state of our patient, we can now proceed with investigation for pituitary and hypothalamic disorders. When there is no clear explanation for hypogonadotropic hypogonadism such as significant physical, nutritional or emotional stress, imaging is indicated to exclude tumors and to help distinguish between pituitary and hypothalamic causes. Magnetic resonance imaging (MRI) with gadolinium contrast is the method of choice due to its sensitivity and accuracy for detection of abnormalities within and near the sella turcica.[10]

A distinct clinical feature of our patient, which clinches diagnosis, is the history of hyposmia. Isolated hypogonadotropic hypogonadism with associated hyposmia or anosmia is characteristic of Kallmann syndrome.[1,3,4] Although most of the Kallmann's syndrome cases are sporadic, three modes of inheritance have been reported: X chromosome-linked (KAL1), autosomal dominant (KAL2) and autosomal recessive (KAL3).[19] The classical X-linked form of the disorder is caused by a variety of genetic mutations in the KAL gene (located on the short arm of the X chromosome, Xp22.3) encoding anosmin-1, a neural adhesion molecule that promotes migration of GnRH neurons and olfactory neurons from the olfactory placode to the hypothalamus during embryonic development.[10]

The features of Kallmann's syndrome can be categorized as reproductive and non-reproductive. The reproductive features for females include delayed puberty and primary amenorrhea, noted in our patient, as well as poorly defined secondary sexual characteristics and infertility. Primary amenorrhea occurs in approximately 90% of cases of idiopathic

hypogonadotropic hypogonadism.[20] Adult females have little or no breast development, although in some patients it may be almost normal.[21] The presence of pubic hair, reflecting a normal adrenarche,[21] helps to distinguish them from those with a constitutional delay of puberty in whom adrenarche typically also is delayed.[10] Girls before puberty have normal stature, but the pubertal growth spurt does not occur. Stature retardation is very rare, but in contrast, the absence of long-bone epiphyseal closure explains these patients' frequent eunuchoid aspect and relative tallness. Our patient claims growth spurt occurring during her early 20's, and such a delay might explain her relative tallness, albeit only 154 cm, in comparison to her family members.

Non-reproductive features include anosmia or hyposmia, unilateral renal aplasia, mirror movements, sensorineural deafness, high-arched palate, eye-movement abnormalities and dental agenesis.[22] Anosmia is commonly missed unless the physician specifically asks or tests for it. However, variants have been described in which the sense of smell is intact or only decreased.[23] Retarded bone maturation, osteopenia and osteoporosis are frequent when the gonadotropin deficiency is discovered in adulthood reflective of estrogen deficiency.[24]

The diagnosis of Kallmann's syndrome is established by the presence of suggestive clinical and laboratory findings consistent with hypogonadotropic hypogonadism and the absence of secondary causes of hypothalamic hypogonadism. The first step in diagnosis is a comprehensive personal and family history, detailed physical examination with astute appraisal secondary sexual characteristics. It is ideal to perform a semiquantitative assessment of olfaction to detect hyposmia or anosmia using a smell identification kit. Body mass index should also be calculated. Laboratory tests should be limited to assessing the levels of LH, FSH, PRL and estradiol. Plasma LH, FSH and estradiol concentrations are often low in women, sometimes being near the detection limit. Plasma estradiol concentrations seem to correlate with breast development. In the absence of breast development, circulating estradiol concentrations are very low to undetectable. While estradiol is detectable with a sensitive assay when breast development exceeds Tanner stage 2,[25] as observed in our patient. Intravenous administration of 100μg GnRH provides no extra diagnostic information relative to baseline gonadotropin levels, but its outcome reflects the severity of the gonadotropin deficiency.[21]

MRI has been useful in the detection of structural abnormalities involving the olfactory tracts,[26,27] optimally visualized using coronal planes. The olfactory bulb is normally seen as well-defined structures along cribriform plate, while the olfactory sulci are seen between gyrus rectus and medial orbital gyrus.[27] High resolution coronal fast spin echo T2-weighted and T1-weighted images are the preferred sequences for morphologic evaluation of the olfactory system.[28-30]

Reported abnormalities include unilateral or bilateral agenesis or hypoplasia of the olfactory bulbs, tracts and sulci.[27,31,32] In a study by Fuerxer,[28] comparing the olfactory bulbs, sulci and frontal lobes in normal versus Kallmann's syndrome patients, the olfactory bulbs were normally located immediately behind the crista galli, measuring 6 to 11 mm in length and 2 to 3.2 mm in width. However, in patients with Kallmann's syndrome, the olfactory bulbs were not visualized and hypoplastic sulci were hardly visible with sizes less than or equal to 1 cm. These findings are analogous to our patient, wherein MRI stated the absence of bilateral olfactory bulbs and shallow olfactory sulci (Figure 5). The ability of MRI to detect morphological anomalies of the olfactory system is particularly useful for patients too young to undergo meaningful testing of olfaction or to test the hypothalamic-pituitary-gonadal axis.[26,27,33]

Pelvic sonography should always be performed to evaluate the uterine size and endometrial thickness, as well as size and follicles of the ovary.[21,34,35,36] The small uterus and ovaries visualized on the patient's ultrasound represents her over-all hypogonadal state (Figure 5). Renal ultrasound examination should be done to exclude renal malformation or agenesis.[21]

In our setting, the following diagnostic tests are readily available: 1) pelvic ultrasound (transvaginal/transrectal/transabdominal), 2) serum FSH, 3) serum estradiol, 4) serum TSH, 5) serum prolactin, 6) serum testosterone, 7) karyotyping and 8) magnetic resonance imaging (MRI). Access to these tests enables us to device an algorithm that could facilitate diagnosis and management of primary amenorrhea (Figure 7). This algorithm (Figure 7) highlights the sequential steps executed in the management of our case.

The choice of therapy is determined by the goal of treatment.[21] Treatment options include sex steroids, gonadotropins and pulsatile GnRH administration. Majority of young women lack development of the secondary sexual characteristics and should be treated with estrogens, commencing at low doses (1mg estradiol). After six months of treatment, when breast development has been optimized, replacement doses of combined estrogen and progesterone should be instituted. Women desirous of pregnancy can be given human menopausal gonadotropin, recombinant FSH and LH for ovarian stimulation.[37,38,39] Intravenous pulsatile administration of GnRH can, likewise, be used with the advantage of mimicking normal cycle dynamics with the resulting ovulation of a single follicle.[40] This therapy offers a clear

hypogonadotropic hypogonadism.[20] Adult females have little or no breast development, although in some patients it may be almost normal.[21] The presence of pubic hair, reflecting a normal adrenarche,[21] helps to distinguish them from those with a constitutional delay of puberty in whom adrenarche typically also is delayed.[10] Girls before puberty have normal stature, but the pubertal growth spurt does not occur. Stature retardation is very rare, but in contrast, the absence of long-bone epiphyseal closure explains these patients' frequent eunuchoid aspect and relative tallness. Our patient claims growth spurt occurring during her early 20's, and such a delay might explain her relative tallness, albeit only 154 cm, in comparison to her family members.

Non-reproductive features include anosmia or hyposmia, unilateral renal aplasia, mirror movements, sensorineural deafness, high-arched palate, eye-movement abnormalities and dental agenesis.[22] Anosmia is commonly missed unless the physician specifically asks or tests for it. However, variants have been described in which the sense of smell is intact or only decreased.[23] Retarded bone maturation, osteopenia and osteoporosis are frequent when the gonadotropin deficiency is discovered in adulthood reflective of estrogen deficiency.[24]

The diagnosis of Kallmann's syndrome is established by the presence of suggestive clinical and laboratory findings consistent with hypogonadotropic hypogonadism and the absence of secondary causes of hypothalamic hypogonadism. The first step in diagnosis is a comprehensive personal and family history, detailed physical examination with astute appraisal secondary sexual characteristics. It is ideal to perform a semiquantitative assessment of olfaction to detect hyposmia or anosmia using a smell identification kit. Body mass index should also be calculated. Laboratory tests should be limited to assessing the levels of LH, FSH, PRL and estradiol. Plasma LH, FSH and estradiol concentrations are often low in women, sometimes being near the detection limit. Plasma estradiol concentrations seem to correlate with breast development. In the absence of breast development, circulating estradiol concentrations are very low to undetectable. While estradiol is detectable with a sensitive assay when breast development exceeds Tanner stage 2,[25] as observed in our patient. Intravenous administration of 100μg GnRH provides no extra diagnostic information relative to baseline gonadotropin levels, but its outcome reflects the severity of the gonadotropin deficiency.[21]

MRI has been useful in the detection of structural abnormalities involving the olfactory tracts,[26,27] optimally visualized using coronal planes. The olfactory bulb is normally seen as well-defined structures along cribriform plate, while the olfactory sulci are seen between gyrus rectus and medial orbital gyrus.[27] High resolution coronal fast spin echo T2-weighted and T1-weighted images are the preferred sequences for morphologic evaluation of the olfactory system.[28-30]

Reported abnormalities include unilateral or bilateral agenesis or hypoplasia of the olfactory bulbs, tracts and sulci.[27,31,32] In a study by Fuerxer,[28] comparing the olfactory bulbs, sulci and frontal lobes in normal versus Kallmann's syndrome patients, the olfactory bulbs were normally located immediately behind the crista galli, measuring 6 to 11 mm in length and 2 to 3.2 mm in width. However, in patients with Kallmann's syndrome, the olfactory bulbs were not visualized and hypoplastic sulci were hardly visible with sizes less than or equal to 1 cm. These findings are analogous to our patient, wherein MRI stated the absence of bilateral olfactory bulbs and shallow olfactory sulci (Figure 5). The ability of MRI to detect morphological anomalies of the olfactory system is particularly useful for patients too young to undergo meaningful testing of olfaction or to test the hypothalamic-pituitary-gonadal axis.[26,27,33]

Pelvic sonography should always be performed to evaluate the uterine size and endometrial thickness, as well as size and follicles of the ovary.[21,34,35,36] The small uterus and ovaries visualized on the patient's ultrasound represents her over-all hypogonadal state (Figure 5). Renal ultrasound examination should be done to exclude renal malformation or agenesis.[21]

In our setting, the following diagnostic tests are readily available: 1) pelvic ultrasound (transvaginal/transrectal/transabdominal), 2) serum FSH, 3) serum estradiol, 4) serum TSH, 5) serum prolactin, 6) serum testosterone, 7) karyotyping and 8) magnetic resonance imaging (MRI). Access to these tests enables us to device an algorithm that could facilitate diagnosis and management of primary amenorrhea (Figure 7). This algorithm (Figure 7) highlights the sequential steps executed in the management of our case.

The choice of therapy is determined by the goal of treatment.[21] Treatment options include sex steroids, gonadotropins and pulsatile GnRH administration. Majority of young women lack development of the secondary sexual characteristics and should be treated with estrogens, commencing at low doses (1mg estradiol). After six months of treatment, when breast development has been optimized, replacement doses of combined estrogen and progesterone should be instituted. Women desirous of pregnancy can be given human menopausal gonadotropin, recombinant FSH and LH for ovarian stimulation.[37,38,39] Intravenous pulsatile administration of GnRH can, likewise, be used with the advantage of mimicking normal cycle dynamics with the resulting ovulation of a single follicle.[40] This therapy offers a clear

advantage over treatment with exogenous gonadotropins, which involves higher rates of both multiple gestation and ovarian hyperstimulation syndrome. For either approach, however, the rate of conception is approximately 30% per ovulation cycle.[41]

Genomic testing for KAL gene or other genetic mutations would provide insight on the mode of inheritance and pathogenesis of the condition. However, these are not available in our setting. Fortunately, the lack of such diagnostic modalities would not hamper appropriate treatment. Regardless of the cause of hypogonadism, the key strategy is to protect our patient from the deleterious effects of hypoestrogenism through estrogen followed by combined estrogen- progesterone therapy. What remains to be done is bone mineral density evaluation to screen for osteoporosis, as well as, renal evaluation to identify other anomalies that may impact her over-all health. Finally, counseling should be part of the therapy to address issues on body image and reproductive function.

In summary, this paper presents a case of Kallmann's syndrome manifesting with classical features of hypogonadotropic hypogonadism and hyposmia, further validated by MRI. For patients like her, treatment is fairly straightforward once diagnosed. The bigger issue is the approach to obtain correct diagnosis, which can be achieved through methodical and perceptive evaluation (Figure 7).

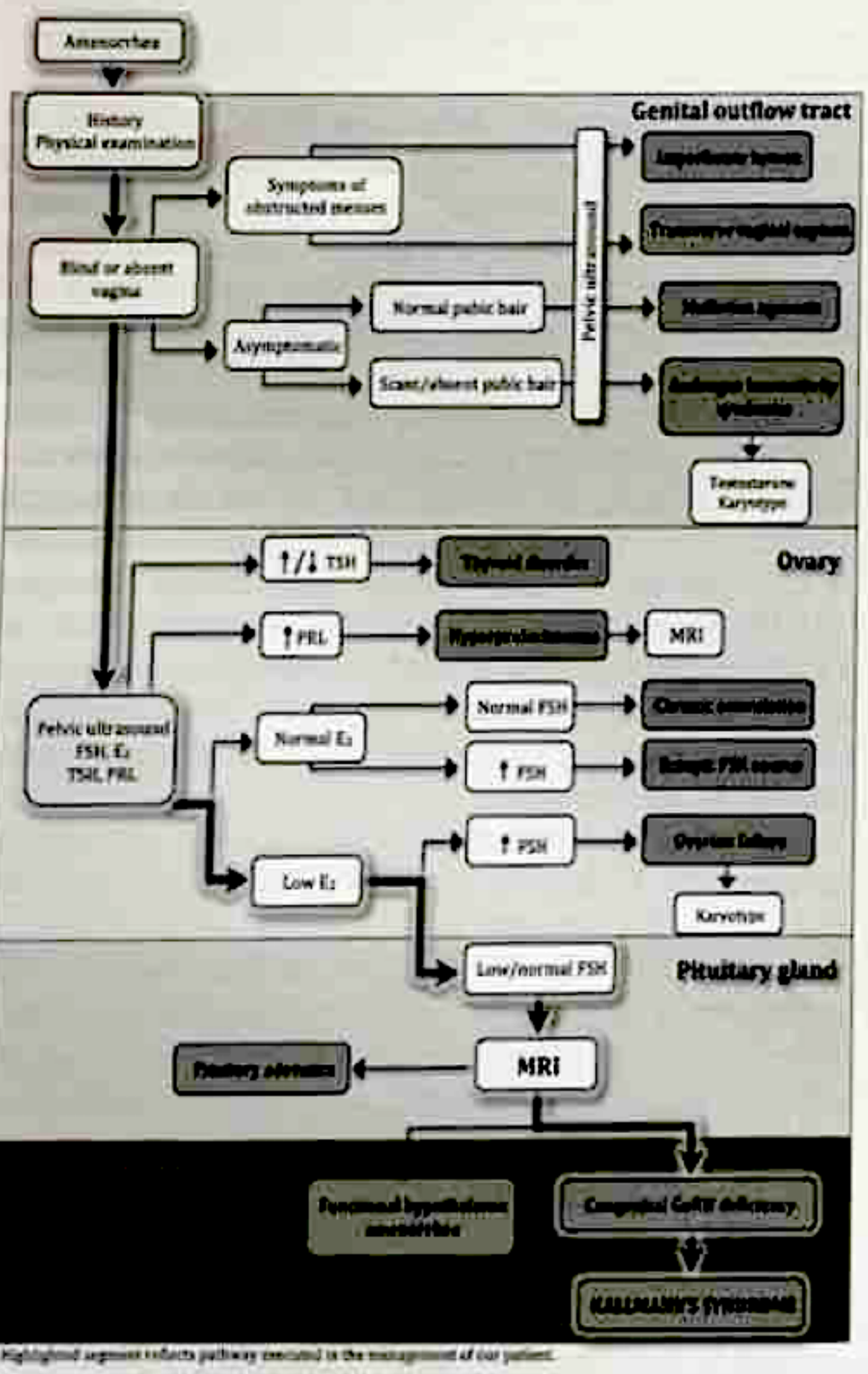

Figure 7. Algorithm in the clinical evaluation of primary amenorrhea.

References

1. Dallago CM, Abech DD, Pererira-Lima JFS, Leães, CGS, Batista RL, Trarbach EB, Oliveira MD. Two cases of Kallmann syndrome associated with empty sella. Pituitary 2008; 11: 109-12.
2. Kallman FJ, Schoenfeld WA, Barrere SE. The genetic aspects of primary eunuchoidism. Am J Ment Defic 1944; 48: 203-36.
3. Buck C, Balasubramanian R, Crowley WF. Isolated Gonadotropin-releasing hormone (GnRH) deficiency), GeneReviews . Seattle (WA): University of Washington, Seattle: 1999-2013. http://www.ncbi.nlm.nih.gov/books/NBK1334
4. Matsuo T, Okamoto S, Izumi Y, Hosokawa A, Takegawa T, Fukui H, et al. A novel mutation of KAL gene in monozygotic twins with Kallmann syndrome. Eur J Endocrinol 2000; 144(6): 783-7.
5. Maestre de San Juan A. Falta total de los nervios olfactorios con anosm ??a en un individuo en quien exist 'a una atrof 'a conge' nita delostest' culosymiembroviril. Siglo Medico 1856; 131: 211.
6. Ribeiro RS, Abucham J. Kallmann syndrome: a historical (corrected) clinical and molecular review. Arq Bras Endocrinol Metabol 2008; 52: 8-17.
7. Deeb A, Robertson A, MacColl G, Bouloux PM, Gibson M, Winyard PJD, Woolf AS, Moghal NE, Cheetham TD. Multicystic dysplastic kidney and Kallmann's syndrome: a new association. Nephrology Dialysis Transplantation 2001; 16: 1170-5.
8. Hardelin J. Kallmann syndrome. Orphanet Encyclopedia. 2005.
9. Doraiswamy M, Potts JM, Axelson DA, et al. MR assessment of pituitary gland morphology in healthy volunteers: age and gender-related differences. Am J Neuroradiol 1992; 13: 1295-9.
10. Speroff L, Fritz MA. Amenorrhea. Clinical Gynecologic Endocrinology and Infertility, 8th edition. 2011: 435-93.
11. World Health Organization. Global data base on body mass index. http://apps.who.int/bmi/index
12. Sloboda DM, Hart R, Doherty DA, et al. Age at menarche: influences of prenatal and postnatal growth. J Clin Endocrinol Metab 2007; 92(1): 46-50.
13. Thomas F, Renaud F, Benefice E, et al. International variability of ages at menarche and menopause: patterns and main determinants. Hum Biol 2001; 73(2): 271-90.

14. Bragg JM, Kuzawa CW, Agustin SS, Banerjee MN, McDade TW. Age at menarche and parity are independently associated with anti-müllerian hormone, a marker of ovarian reserve, in Filipino young adult women. Am J Hum Biol 2012; 1-7.
15. Al-Sahab B, Adair L, Hamadeh MJ, Ardern CI, Tamim H. Impact of breastfeeding duration on age at menarche. Am J Epidemiol 2011; 1-7.
16. Current evaluation of amenorrhea. The Practice Committee of the American Society for Reproductive Medicine. Fertil Steril 2008; 90: S219-5.
17. World Health Organization. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. The Lancet 2004; 363: 157-63.
18. World Health Organization. The Asian Pacific perspective: redefining obesity and its treatment. 2000; 20.
19. Hermanussen M, Sippell WG. Heterogeneity of Kallmann's syndrome. Clin Genet 1985; 28: 106-11.
20. Young J, Vincent D, Bachelot A, et al. Congenital hypogonadotrophic hypogonadism in women: 1) clinical presentation, hormonal evaluation, 2) ovarian morphological and genetic studies in a series of 104 patients. A multicenter survey. In XXIII Congre's de la Socie 'te ' Franc 'aise d'Endocrinologie. Montpellier 2006.
21. Skalba P, Guz M. Hypogonadotropic hypogonadism in women. Polish J Endocrinol 2011; 62 (6).
22. Tsai PS, Gill JC. Mechanisms of disease: Insights into X-linked and autosomal-dominant Kallmann syndrome. Nat Clin Pract Endocrinol Metab 2006; 2(3): 160-71.
23. Jenkin A, Renner D, et al. A case of primary amenorrhea, diabetes and anosrnia. Gynecol Endocrinol 2000; 14: 65-70.
24. Semple RK, Kemal Topaloglu A. The recent genetics of hypogonadotrophic hypogonadism - novel insights and new questions. Clin Endocrinol 2010; 72: 427-35.
25. Brioude F, Bouligand J, Trabado S, et al. Non-syndromic congenital hypogonadotropic hypogonadism: clinical presentation and genotype-phenotype relationships. Eur J Endocrinol 2010; 162: 835-51.
26. Quinton R, Beirne P, Bouloux PMG, Stanhope RG, Conway GS. Routine neuroimaging in classical isolated gonadotropin deficiency is of limited clinical value. Clin Endocrinol 2001; 54(1): 127- 9.
27. Madan R, Sawlani V, Gupta S, Phadke RS. MRI findings in Kallmann syndrome. Neurol India 2000; 52(4): 501-3.
28. Fuerxer F, Carlier R, Iffenecker C, Schaison G, Doyon D. Magnetic resonance imaging of the olfactory pathways in Kallmann de Morsier syndrome. J Neuroradiol 1996; 23: 223-30.
29. Freitas P, Carvalho S, Ribeiro F, Marnoto D, Martins F. Neuroradiology of Kallmann's syndrome. Acta Med Port 2001; 14: 123-6.
30. Munez A, Dieguez E. A plea for proper recognition: the syndrome of Maestre de San Juan-Kallman. Am J Neuroradiol 1997; 18: 1395-6.
31. Quinton R, Duke VM, Zoysa PA, Platts AD, Valentine A, Kendall B, et al. The neuroradiology of Kallmann's syndrome: a genotypic and phenotypic analysis. J Clin Endocrinol Metab 2004; 81(8): 3010-7.
32. Vogl TJ, Stemmler J, Heye B, Schopohl J, Danek A, Bergman C, et al. Kallmann syndrome versus idiopathic hypogonadotrophic hypogonadism at MR imaging. Radiology 2004; 191: 53-7.
33. Massin N, Pe'cheux C, Eloit C, Bensimon JL, Galey J, Kuttenn F et al. X chromosome-linked Kallmann syndrome: clinical heterogeneity in three siblings carrying an intragenic deletion of the Kal-1 gene. J Clin Endocrinol Metab 2003; 88(5): 2003-8.
34. Schoot DC, Coelingh Bennink HJ, Mannaerts BM, Lamberts SW, Bouchard P, Fauser BC. Human recombinant follicle-stimulating hormone induces growth of preovulatory follicles without concomitant increase in androgen and estrogen biosynthesis in a woman with isolated gonadotropin deficiency. J Clin Endocrinol Metab 1992;74: 1471-3.
35. Tsilchorozidou T, Conway GS. Uterus size and ovarian morphology in women with isolated growth hormone deficiency, hypogonadotrophic hypogonadism and hypopituitarism. Clin Endocrinol 2004; 61: 567-72.
36. Kottler ML, Chou YY, Chabre O, Richard N, Polge C, Brailly-Tabard S, et al. A new FSH {beta} mutation in a 29-year-old woman with primary amenorrhea and isolated FSH deficiency: functional characterization and ovarian response to human recombinant FSH. Eur J Endocrinol 2010;162: 633-41.
37. Chryssikopoulos A, Gregoriou 0 ,Papadias C, et al. Gonadotropin ovulation induction and pregnancies in women with Kallmann's syndrome. Gynecol Endocrinol 1998; 12: 103-8.
38. Sungurtekm U, Fraser IS, Shearman RP. Pregnancy in women with Kallmann's syndrome. Fertil Steril 1995; 63: 494-9.
39. Kousta E, White DM, Piazzi A, et al. Successful induction ovulation and completed pregnancy using recombinant human luteinizing hormone and follicle stimulating hormone in a woman with Kallmann's syndrome. Hum Reprod 1996; 11: 70-1.
40. Swenne I, Thurfjell B. Clinical onset and diagnosis of eating disorders in premenarcheal girls is preceded by inadequate weight gain and growth retardation. Acta Paediatrica 2003; 92: 1133-7.
41. Brioude F, Bouligand J, Trabado S, et al. Non-syndromic congenital hypogonadotropic hypogonadism: clinical presentation and genotype-phenotype relationships. Eur J Endocrinol 2010;162: 835-51.