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Management of Hypogonadism in Adolescent Girls and Adult Women With Prader–Willi Syndrome

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Prader–Willi syndrome (PWS) is a neurodevelopmental disorder characterized by an insatiable appetite, dysmorphic features, cognitive and behavioral difficulties, and hypogonadism. The heterogeneous reproductive hormone profiles indicate that some PWS women may have symptoms of hypoestrogenism, while others may potentially be fertile. We describe our experience in the assessment and treatment of hypogonadism in adolescents and adult females with PWS. The study population consisted of 20 PWS females, age $\geq$16 years (27.3 $\pm$ 7.9 years), followed in our clinic (12 deletion, 7 uniparental disomy, 1 imprinting-center defect). General physical examination, pubertal assessment, body mass index (BMI), gynecological examination, ultrasonography, bone densitometry, and hormonal profiles [FSH, LH, inhibin B, estradiol, prolactin, and TSH] were performed. The relevant assessed factors were: FSH and inhibin B, menstrual cycles (oligo/amenorrhea or irregular bleeding), ultrasound findings (endometrial thickness, uterine/ovarian abnormalities), BMI, bone densitometry, and patient/caregivers attitude. We classified seven women with inhibin B >20 ng/ml as potentially fertile. Following the assessment of the above factors, we recommended the individual-specific treatment; contraceptive pills, intra-uterine device, estrogen/progesterone replacement, and cyclic progesterone, in 3, 1, 4, and 1 patients, respectively. Four patients did not follow our recommendations due to poor compliance or family refusal. We recommended contraception pills for one 26-year-old woman with inhibin B and FSH levels 53 ng/ml and 6.4 IU/L; however, she refused treatment, conceived spontaneously and had an abortion. Guidelines for hormonal replacement therapy in PWS need to be tailored individually depending on physical development, hormonal profiles, bone density, and emotional and social needs of each PWS adolescent and adult.

Key words: Prader–Willi syndrome; hypogonadism; contraception; hormone replacement therapy

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INTRODUCTION

Prader–Willi syndrome (PWS), a complex neurogenetic disorder is characterized by dysmorphic features, major cognitive and behavioral difficulties, and hypogonadism [Goldstone et al., 2008; Cassidy and Driscoll, 2009].

In PWS infant girls, genital hypoplasia, specifically small clitoris and underdeveloped labiae, are commonly seen as manifestations of hypogonadism [Crino et al., 2003; Cassidy and Driscoll, 2009].

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Most PWS girls have delayed and/or incomplete pubertal development, although some cases of precocious puberty have been described [Pusz and Rotenstein, 2008]. Some females undergo spontaneous menarche but most have primary or secondary amenorrhea or oligomenorrhea [Crino et al., 2003; Diene et al., 2010; Eldar-Geva et al., 2010]. However, five pregnancies have been reported in three women with genetically documented PWS [Akefeldt et al., 1999; Schulze et al., 2001] and seven pregnancies were reported in two women in whom PWS was diagnosed only by clinical criteria before the genetics of PWS had been delineated [Laxova et al., 1973]. Another woman with chromosome 15q11–q13 deletion gave birth to two children [Hockey, 1986]. Even though hypogonadism is a cardinal feature of PWS, sexual interests and experiences are common among PWS adolescents and adults [Gross-Tsur et al., 2011].

Variable combinations of primary gonadal defect and hypothalamic dysfunction contribute to the hypogonadism in subjects with PWS [Eiholzer et al., 2006; Brandau et al., 2008; Hirsch et al., 2009; Eldar-Geva et al., 2009, 2010; Siemensma et al., 2012]. In a cohort of adolescents and adults with PWS, we characterized four distinct patterns of gonadal dysfunction based on FSH and inhibin B levels: hypergonadotrophic (primary gonadal) hypogonadism, hypogonadotrophic (central/hypothalamic) hypogonadism, partial gonadal and central dysfunction and mild central with severe gonadal dysfunction [Gross-Tsur et al., 2011]. We suggested using serum inhibin B as the most reliable marker of gonadal function in adolescent girls and adult women with PWS [Eldar-Geva et al., 2010].

The wide spectrum of reproductive hormone profiles indicates that some PWS women may suffer from symptoms of hypoestrogenism, while others may potentially be fertile. Despite recent progress in characterizing the heterogeneity in hormonal patterns among hypogonadal PWS women, specific guidelines for treating this population have not been reported. We describe here our experience in the management of hypogonadism in adolescent girls and adult women with PWS.

PATIENTS AND METHODS

Of the 129 patients (ages 2 months to 47 years; 65 females, 64 males) with genetically confirmed PWS in Israel, almost all are treated in the National Multidisciplinary PWS clinic in Shaare Zedek Medical Center, Jerusalem. In this report, we describe our experience in the assessment and treatment of hypogonadism in adolescents and adult females with PWS. The study population consisted of 20 females, age $\geq$16 years, followed in our clinic: mean $\pm$ SD age was 26.8 $\pm$ 7.9 years, height 147 $\pm$ 5.4 cm, and body mass index (BMI) 33.3 $\pm$ 12.4 kg/m^2. The clinical diagnosis of PWS was confirmed by DNA methylation analysis. Deletion of paternal 15q11.2–13 (DEL) was found in 12 individuals, 7 had maternal UPD at the same loci and 1 had an imprinting center defect.

Four women had diabetes mellitus; two were treated with insulin and two with metformin. Two of them also received statins because of hypercholesterolemia. One woman with hypothyroidism was treated with L-thyroxine and one received montelukast for asthma. Other medications included risperdone in five women, selective serotonine-reuptake inhibitors (SSRIs) in five, topiramate in two, propericiazine in two; carbamazepine, ziprasidone, omeprazole, and furosemide were taken by one patient each. One woman, aged 23 years, had received growth hormone several years before evaluation in our study.

Clinical assessment included a general physical examination, height and weight measurements and Tanner classification of pubertal status [Tanner, 1962; Carel and Léger, 2008]. Gynecological examination, performed by an experienced, female gynecologist (TEG), included inspection of the external genitalia, and when possible, gentle bimanual vaginal examination. Two women refused any gynecological examination or inspection.

Bone mineral densitometry (BMD) measurements were performed (Discovery 4500A; Hologic, Bedford, MA) as part of routine follow-up in our clinic. BMD was recorded as well as Z-scores (compared to sex- and age-matched healthy controls) at left femoral neck, total left hip and lumbar spine. For qualitative analysis, a Z score of -1.0 to -2.5 was considered to be osteopenia and osteoporosis was defined as a Z score <-2.5).

Evaluation of IQ was performed individually between the ages of 6–16 years. Each patient underwent a standardized test. When appropriate, the Wechsler Preschool & Primary Scale of Intelligence (WPSSI), the Wechsler Intelligence Scale for Children-Revised (WISC-R), the Kaufman Assessment Battery for Children (K-ABC), and the Leiter International Performance Scale-Revised (Leiter-R), a non-verbal test, were administered.

Serum concentrations of LH, FSH, inhibin B, estradiol, TSH, and prolactin were measured as previously described [Eldar-Geva et al., 2009].

When all of the test results were available, the medical team met with each patient and their parents/caregivers. Patients were asked if they had or desired to have sexual experiences or interests. Recommendations for treatment or follow-up were presented after which the benefits and possible side effects of the management plan were explained. The final decisions were based on mutual consensus.

RESULTS

As described in our previous study [Gross-Tsur et al., 2012], we assigned each patient to one of four hypogonadal groups, according to the relative contribution of central (hypothalamic) and primary ovarian dysfunction, based on FSH and inhibin B levels (Table I). Serum inhibin B levels were low in all, except for women in Group C whose levels were in the low–normal range, indicating some degree of ovarian function, albeit less than expected for their age. The women in Group C were older than the other women [ages (mean $\pm$ SD), 31.5 $\pm$ 8.4 vs. 24.2 $\pm$ 6.5 years; $P = 0.042$]. Genetic subtypes, BMI, IQ, sexual maturity (breast and pubic hair Tanner stages), labial development, and menstrual status (relative frequencies of amenorrhea, oligomenorrhea and irregular vaginal spotting) were similar among the groups. Inspection of the external genitalia revealed poor hygiene in five women, of whom four had vulvovaginitis, one of them was diabetic.

BMD showed that reduced density of the femoral neck and/or lumbar spine in 15 out of 19 measurements, 8 with osteopenia and 7 with osteoporosis (Table I). BMD parameters were similar among the groups.

TABLE I. Demographic and Clinical Data in 20 Adolescent and Adult Women With PWS

Group	A (n = 1)	B (n = 5)	C (n = 7)	D (n = 7)
Hypothalamic—ovarian function	Normal—hypo (FSH > 15, INB < 10)	Hypo—hypo (FSH < 0.5, INB < 10)	Partial—partial (FSH 1.5–15, INB > 20)	Partial—hypo (FSH 1.5–15, INB < 10)
Genetics: DEL/UPD/ICD	1/0/0	2/2/1	4/2/0	4/3/0
Age (median; range)	19.9	26.8; 16–31.4	26.7; 23.9–47	21.3; 16.4–35.6
BMI (median; range)	31.2	32.4; 29.1–74	27.3; 21.8–37.6	30.7; 21.8–49.6
Menstrual status				
Amenorrhea	1	2	1	5
Oligomenorrhea		3	4	1
Irregular vaginal spotting			2	1
Sexual development				
Breast Tanner stage	4	4; 4–5	5; 2–5	5; 2–5
Pubic hair tanner stage	4	4; 3–5	4; 2–5	4; 3–5
Normal/hypoplastic labia	0/1	2/3	4/3	2/3[a]
Densitometry				
Normal	1		2[b]	1
Osteopenia		3	1	4
Osteoporosis		2	3	2
IQ (median; range)	55	69; 60–100[c]	77.5; 50–100[d]	70; 50–100

[a]Five subjects had genital examination, the other two refused.
[b]Available for six patients.
[c]Available for four patients, one woman had mild intellectual disability without formal IQ testing.
[d]Available for six patients; one woman had mild to moderate intellectual disability.

Hormonal characteristics and clinical features which we considered when deciding on specific treatment recommendations for each patient are presented in Table II. The various treatment options are shown in Table III. Three women (aged 23, 26 and 27 years) reported having sexual relations and one (25-year-old) stated that she planned to start. We recommended specific treatment for each individual taking into account the clinical features and hormonal profiles described in Table II. Specifically, from the seven women in group C, we recommended contraceptive pills for three women aged 23–27. The caregivers of a 26-year-old woman reported having intimate relations with men in the residential home where she lived. We prescribed an IUD for this woman. In four women, our treatment recommendations were not implemented, however, due to poor compliance and/or parental objections to administering hormonal or contraceptive medications.

TABLE II. Relevant Factors to Be Assessed in Hypogonadal Adolescent and Adult Females With PWS

1. Ovarian function:
   a. Fertility possible (Group C)
   b. Ovarian failure (Groups A, B, D)
2. Menstrual cycles:
   a. Amenorrhea
   b. Oligomenorrhea
   c. Abnormal vaginal bleeding (meno-metrorrhagia)
3. Ultrasound findings:
   a. Endometrial thickness
   b. Any uterine/ovarian abnormalities (e.g., fibroids, ovarian cysts)
4. BMI:
   a. Low/normal
   b. Overweight/obese
5. Densitometry:
   a. Osteoporosis
   b. Osteopenia or normal
6. Other indication/contra-indications (e.g., hirsutism, family history of thrombophilia)
7. Patient/familial (caregivers) attitude

TABLE III. Treatment Options

1. Hormone replacement treatment (HRT)—estrogen and progesterone
2. Cyclic progesterone
3. Contraception:
   a. Contraceptives pills
   b. IUD
4. Non-hormonal treatment to prevent osteoporosis (vitamin D and calcium)
5. No treatment:
   a. No indication/contraindication
   b. Objection (family or patient)

We advised a 26-year-old woman, with deletion of 15q11–q13, whose hormonal profile was typical of Group C, including levels of inhibin B levels 53 pg/ml and FSH 6.4 IU/L to take oral contraceptives. She had undergone spontaneous menarche at age 16 followed by oligomenorrhea. Breast and pubic hair Tanner stages were 4, her height 145 cm, BMI was 23.3 kg/m^2 and her IQ tests were within the normal range. She reported having sexual relationships with several partners. Despite our recommendations, she refused any form of contraception. About 1 year later she conceived spontaneously and requested termination of the pregnancy. Following an induced abortion, the patient continued to refuse any contact with our clinic claiming that "she is not PWS."

One serious complication occurred in a 25-year-old woman in Group C, for whom a low-dose contraceptive, YAZ (ethynilestradiol 0.02 mg/drospirenone 3 mg, Schering GmbH, Bayer, Israel) was prescribed when she described having sexual relations. Family history was uneventful, specifically, no thrombo-embolic events or high blood pressure were noted. During an international flight she complained of chest pain and later was diagnosed as having a pulmonary embolism. The contraceptive pill was discontinued and low-molecular weight heparin was administered for 1 year. One year following that event the patient is healthy with no sequelae. No other major or minor side effects were recorded.

DISCUSSION

Designing individualized treatment for hypogonadism in PWS women is a major therapeutic challenge. Endocrinologists and gynecologists need to take into account the many variations in clinical phenotypes and hormonal patterns seen in this syndrome. The variability of the hypogonadism results from several combinations of primary ovarian defects and hypothalamic dysfunction, systemic factors such as osteoporosis which in PWS is common even in adolescents individuals [Höybye et al., 2002; Sinnema et al., 2011; Jørgensen et al., 2013], obesity which can be morbid, GH deficiency and the use of psychiatric medications. In addition, behavioral and cognitive problems, low compliance and the fact that most of the adult females live in residential homes should be taken into consideration. In view of the physical and psycho-social consequences of hypogonadism in this population and their interest in sexual and romantic issues [Gross-Tsur et al., 2011] hormonal treatment for affected individuals needs to be considered. However, no guidelines for treating the hypogonadism in females with PWS have been published.

We recommend that hormonal replacement therapy in adolescent girls and adult women with PWS be tailored individually depending mainly on the specific hypogonadal phenotype. Assessment of specific hormonal data, particularly inhibin B, is essential. We consider inhibin B levels >20 pg/ml to be a marker of significant ovarian function (found in 7/20 women in our series) and suggests some degree of potential fertility. In spite of their hypogonadism, adolescents and adults with PWS express a strong interest in sexual and romantic thoughts and activities; some reported having "romantic" or even sexual relationships with boyfriends [Gross-Tsur et al., 2011]. Since pregnancy and particularly motherhood are unfeasible in women with PWS, we recommended contraception for those women who may be sexually active or have "romantic" interests, unless contraindicated. One of our PWS patients, whose inhibin B level (53 pg/ml) was in the range considered to indicate reasonable ovarian reserve even for a normal population [Sehested et al., 2000; Kwee et al., 2008], refused any type of contraception, became pregnant following unprotected intercourse, and at her request, underwent termination of the pregnancy. This case supports the use of measuring inhibin B in PWS women in order to assess potential fertility. The possibility that PWS women might need contraception should be considered and discussed with the patient or her guardians. Non-hormonal contraception methods, such as intrauterine device should be considered if estrogen treatment is contraindicated (e.g., thrombophilia, high blood pressure, etc.). Counseling about vulvo-vaginal hygiene and prevention of sexually transmitted diseases should be provided.

Analyzing the hormonal data, together with consideration of other parameters such as menstrual status and BMI, may enable us to tailor specific hormone replacement treatment (HRT) for women with PWS. Cyclic progesterone may be indicated for those with irregular vaginal bleeding or oligomenorrhea and normal estradiol levels, particularly in obese women or those with abnormal or thick endometrium diagnosed using ultrasonography. Vaginal bleeding in this population does not necessarily indicate ovulation or ovarian steroid secretion, since aromatization of adrenal steroids to estrogens in adipose tissue may trigger pseudo-pubertal development, endometrial estrogenisation and breakthrough bleeding. Progestin would overcome the unopposed estrogenic effect on the endometrium and will prevent endometrial hyperplasia and cancer.

Combined estrogen/progesterone treatment is suggested for women with amenorrhea and low estradiol levels. In a previous study, only 43% of PWS females were interested in receiving hormonal medication to achieve regular menstruation [Gross-Tsur et al., 2011]. Such combined estrogen/progesterone treatment is particularly important in those with low or normal BMI or decreased BMD.

Although all of our PWS patients are treated with vitamin D and calcium supplements, low BMD is very common (Table I) even in adolescent girls and young women. Growth hormone deficiency, low physical activity and limited weight bearing, long-standing hypotonia, anticonvulsive medications and other unknown factors may contribute to the high prevalence of abnormal BMD in this population. Although higher doses of vitamin D and calcium, together with scheduled exercises are the first-line treatment in PWS subjects, HRT may help to prevent osteoporosis, bone fractures and other consequences of prolonged hypoestrogenism.

We chose not to recommend any specific treatment in 11/20 of our patients. Reasons for not recommending treatment included amenorrhea, combined with thin endometrium, normal (or near normal) BMI, undetectable inhibin B and normal or near normal BMD. No treatment was advised for some individuals with moderate to severe intellectual disability with no romantic and sexual interests or activity.

Four PWS women (20%) did not follow our recommendations (Table IV)—one did not use hormonal contraception (and conceived) and three did not use combined HRT consistently. In two of these cases, their strictly religious families refused any hormonal treatment.

The known side effects and complications of contraceptive pills and hormone replacement therapy should also be considered in

TABLE IV. Intention to Treat and Actual Treatment in 20 Adolescent and Adult Females With PWS

Treatment	Intention	Actual
Contraceptive pills	3	2
Contraceptive IUD	1	1
HRT estrogen + progesterone	4	1
Cyclic progesterone	1	1
Non-hormonal treatment of decreased BMD	All	All
No specific treatment recommended	11	15

each case and be discussed with the patient and her family/caregivers. Family history of breast or ovarian cancer or thrombophilia should be considered as contraindications to HRT. The individual advantages and disadvantages of the recommended therapy should be discussed.

In summary, most PWS females show clinical and/or laboratory evidence of hypogonadism affecting their appearance, medical condition, and quality of life. In adolescent girls and adult women with PWS, determining individual reproductive hormone profiles, particularly inhibin B levels, may be important for assessing potential fertility. Appropriate hormone replacement, or contraception when indicated, should be considered. Hormone replacement therapy is likely to improve BMD and may have beneficial effects on body image and quality of life. A prospective longitudinal study of HRT for females with PWS including effects on osteoporosis, body image, behavior, and quality of life is needed.

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REFERENCES

Akefeldt A, Törnhage CJ, Gillberg C. 1999. A woman with Prader–Willi syndrome gives birth to a healthy baby girl. Dev Med Child Neurol 41: 789–790.

Brandau DT, Theodoro M, Garg U, Butler MG. 2008. Follicle stimulating and leutinizing hormones, estradiol and testosterone in Prader–Willi syndrome. Am J Med Genet Part A 146A:665–669.

Carel JC, Léger J. 2008. Precocious puberty. N Engl J Med 358:2366–2377.

Cassidy SB, Driscoll DJ. 2009. Prader–Willi syndrome. Eur J Hum Genet 17:3–13.

Crino A, Schiaffini R, Ciampalini P, Spera S, Beccaria L, Benzi F, Bosio L, Corrias A, Gargantini L, Salvatoni A, Tonini G, Levieri C. Genetic Obesity Study Group of Italian Society of Pediatric endocrinology and diabetology (SIEDP). 2003. Hypogonadism and pubertal development in Prader–Willi syndrome. Eur J Pediatr 162:327–333.

Diene G, Mimoun E, Feigerlova E, Caula S, Molinas C, Grandjean H, Tauber M, French Reference Centre for PWS. 2010. Endocrine disorders in children with Prader–Willi syndrome–Data from 142 children of the French database. Horm Res Paediatr 74:121–128.

Eiholzer U, L'Allemand D, Rousson V, Schlumpf M, Gasser T, Girard J, Grüters A, Simoni M. 2006. Hypothalamic and gonadal components of hypogonadism in boys with Prader-Labhart-Willi syndrome. J Clin Endocrinol Metab 91:892–898.

Eldar-Geva T, Hirsch HJ, Rabinowitz R, Benarroch F, Rubinstein O, Gross-Tsur V. 2009. Primary ovarian dysfunction contributes to the hypogonadism in women with Prader–Willi syndrome. Horm Res 72:153–159.

Eldar-Geva T, Hirsch HJ, Benarroch F, Rubinstein O, Gross-Tsur V. 2010. Hypogonadism in females with Prader–Willi syndrome from infancy to adulthood: Variable combinations of a primary gonadal defect and hypothalamic dysfunction. Eur J Endocrinol 162:377–384.

Goldstone AP, Holland AJ, Hauffa BP, Hokken-Koelega AC, Tauber M. 2008. Recommendations for the diagnosis and management of Prader–Willi syndrome. J Clin Endocrinol Metab 93:4183–4197.

Gross-Tsur V, Eldar-Geva T, Benarroch F, Rubinstein O, Hirsch HJ. 2011. Body image and sexual interests in adolescents and young adults with Prader–Willi syndrome. J Pediatr Endocrinol Metab 24:469–475.

Gross-Tsur V, Hirsch HJ, Benarroch F, Eldar-Geva T. 2012. The FSH-inhibin axis in Prader–Willi syndrome: Heterogeneity of gonadal dysfunction. Reprod Biol Endocrinol 6:39.

Hirsch HJ, Eldar-Geva T, Benarroch F, Rubinstein O, Gross-Tsur V. 2009. Primary testicular dysfunction is a major contributor to abnormal pubertal development in males with Prader–Willi syndrome. J Clin Endocrinol Metab 94:2262–2268.

Hockey A. 1986. X-linked intellectual handicap and precocious puberty with obesity in carrier females. Am J Med Genet 23:127–137.

Höybye C, Hilding A, Jacobsson H, Thorén M. 2002. Metabolic profile and body composition in adults with Prader–Willi syndrome and severe obesity. J Clin Endocrinol Metab 87:3590–3597.

Jørgensen AP, Ueland T, Sode-Carlsen R, Schreiner T, Rabben KF, Farholt S, Høybye C, Christiansen JS, Bollerslev J. 2013. Two years of growth hormone treatment in adults with Prader–Willi syndrome do not improve the low BMD. J Clin Endocrinol Metab 98:E753–E760. February 22 [Epub ahead of print].

Kwee J, Schats R, McDonnell J, Themmen A, de Jong F, Lambalk C. 2008. Evaluation of anti-Mullerian hormone as a test for the prediction of ovarian reserve. Fertil Steril 90:737–743.

Laxova R, Gilderdale S, Ridler MAC. 1973. An aetiological study of fifty-three female patients from a subnormality hospital and of their offspring. J Ment Defic Res 17:193–225.

Pusz ER, Rotenstein D. 2008. Treatment of precocious puberty in a female with Prader–Willi syndrome. J Pediatr Endocrinol Metab 21:495–500.

Schulze A, Mogensen H, Hamborg-Petersen B, Graem N, Ostergaard JR, Brøndum-Nielsen K. 2001. Fertility in Prader–Willi syndrome: A case report with Angelman syndrome in the offspring. Acta Paediatrica 90:455–459.

Sehested A, Juul AA, Andersson AM, Petersen JH, Jensen TK, Miller J, Skakkebaek NE. 2000. Serum inhibin A and inhibin B in healthy prepubertal, pubertal, and adolescent girls and adult women: Relation to age, stage of puberty, menstrual cycle, follicle-stimulating hormone, luteinizing hormone, and estradiol levels. J Clin Endocrinol Metab 85:1634–1640.

Siemensma EP, van Alfen-van der Velden AA, Otten BJ, Laven JS, Hokken-Koelega AC. 2012. Ovarian function and reproductive hormone levels in girls with Prader–Willi syndrome: A longitudinal study. J Clin Endocrinol Metab 97:E1766–E1773.

Sinnema M, Maaskant MA, van Schrojenstein Lantman-de Valk HM, van Nieuwpoort IC, Drent ML, Curfs LM, Schrander-Stumpel CT. 2011. Physical health problems in adults with Prader–Willi syndrome. Am J Med Genet Part A 155A:2112–2124.

Tanner JM. 1962. Growth at adolescence, 2nd edition. Oxford, UK: Blackwell Scientific. pp 88–102.