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Gonadal Hormone Substitution in People with Prader-Labhart-Willi Syndrome: An International Prader-Willi Syndrome Organisation Survey

Urs Eiholzer[a] Anika Stephan[a] Christiane Fritz[a] Claudia Katschnig[a] Cees Noordam[a, b] on behalf of the Clinical and Scientific Advisory Board of the International Prader-Willi Syndrome Organisation (IPWSO)

[a]Centre for Paediatric Endocrinology Zurich (PEZZ), Zurich, Switzerland; [b]Department of Pediatrics, Radboud University Medical Centre, Nijmegen, The Netherlands

Keywords
Prader-Willi syndrome · Hypogonadism · Hormone replacement therapy · Puberty · Behaviour

Abstract
Background: Prader-Labhart-Willi syndrome (PWS) is a rare genetic disorder characterized by intellectual disability, behavioural problems, hypothalamic dysfunction, and specific dysmorphisms. Hypothalamic dysfunction causes growth hormone deficiency, dysregulation of energy balance, and hypogonadism. Although hypogonadism is prevalent in PWS, there are no clear guidelines for diagnosis and treatment. In particular, gonadal hormone substitution is a matter of debate due to concerns associated with the potentially induced aggressive behaviour, foremost in males, by sex steroids. ***Methods:*** In 2019, a workshop dedicated to hypogonadism was held prior to the 10th International PWS Organization Conference. In this context, we designed a questionnaire to assess "the current standard of care" of hypogonadism in children and adults with PWS, which was sent out to physicians caring for people with PWS worldwide. ***Results:*** Responses were received from a total of 24 centres located in 19 countries. Participating centres treat a total number of at least 1,000 children and adults with PWS. Responses showed limited consensus on who should be treated or at what age treatment should commence. Remarkably, very few behavioural problems were attributed to hormone substitution. ***Conclusion:*** Based on our findings, we make recommendations to progress the knowledge on hypogonadism in PWS and improve daily practice.

Introduction

Prader-Labhart-Willi syndrome (PWS) is a rare genetic disorder resulting from a lack of expression of the paternally derived chromosome, 15q11-q13. PWS is characterized by intellectual disability, behavioural problems, and hypothalamic dysfunction combined with specific

Clinical and Scientific Advisory Board of the International Prader-Willi Syndrome Organisation (IPWSO): Moris Angulo, Susanne Blichfeldt, Suzanne Cassidy, Daniel Driscoll, Marilyn Dumont-Driscoll, Urs Eiholzer, Janice Forster, Tony Holland, Charlotte Höybye, Marguerite Hughes, Shuan-Pei Lin, Ann Scheimann, Maité Tauber, Harold van Bosse.

karger@karger.com
www.karger.com/hrp

Correspondence to:
Urs Eiholzer, urs.eiholzer@pezz.ch

Table 1. Survey respondents by continent and the centre size (based on the PWS patient number currently undergoing treatment)

Continent	Centre size					*N*
	1–10 (*n* = 3)	11–30 (*n* = 8)	31–50 (*n* = 5)	51–100 (*n* = 4)	100+ (*n* = 7)	
Asia	–	1	1	–	1	3
Australia/Oceania	1	1	1	–	–	3
Europe	2	5	3	1	5	16
North America	–	–	–	2	1	3
South America	–	1	–	1	–	2

PWS, Prader-Labhart-Willi syndrome.

dysmorphisms [1, 2]. Hypothalamic dysfunction causes growth hormone deficiency, hypogonadism, and a dysregulation of energy balance with hypoactivity and insatiable hunger, which results in increased fat mass and decreased muscle mass. Current treatment regimens include controlling nutrient intake and increasing activity along with early growth hormone therapy. The beneficial effects of early growth hormone deficiency therapy in PWS have been demonstrated: short stature is normalized and muscle mass enhanced [3–5]. Hypogonadism is apparent in males with micropenis and cryptorchidism at birth and sexual maturation stopping in most cases by early to mid-puberty [6]. Conversely, the findings in girls are less obvious; in many cases an almost complete maturation and breast development occurs, partly because of the aromatization of androgens in the fat tissue. However, spontaneous menarche is rather unusual [7]. Where growth hormone therapy has been broadly accepted as a standard treatment in PWS, gonadal hormone substitution remains a matter of debate since the early 1990s. This is mainly because of the concerns associated with the potential induction of aggressive behaviour, foremost in males, caused by this type of substitution. Nevertheless, gonadal substitution is considered the most effective way to improve muscle mass in men. For both sexes, hormone substitution can also create an adult appearance, while preventing osteopenia and osteoporosis, and hence is important to the overall health and quality of life in PWS [7]. Yet the number of studies on gonadal substitution in PWS is limited [6, 8, 9]. Based on observational studies and expert opinion, there are only a small number of published recommendations on sex steroid supplementation in PWS, particularly regarding the age of treatment onset. The recommended age for starting gonadal replacement therapy varies from 14 to 16 years in boys and 11 to 16 years in girls [7, 10, 11]. The paucity of both clinical studies and expert opinion hampers the development of consensus on the treatment of hypogonadism in this rare disease. With the high prevalence of hypogonadism in PWS [12], treating physicians require guidance as to when and how to treat their patients based on "the standard of care". To meet this need, we designed a questionnaire to examine the current treatment methods for hypogonadism in children, adolescents, and adults with PWS. On behalf of the International PWS Organisation (IPWSO), the survey was sent out to physicians caring for people with PWS worldwide, as part of a workshop dedicated to hypogonadism that was held prior to the 10th IPWSO 2019 conference in Cuba. The primary goal was to gain insight into current treatment practices, noting the similarities in beliefs, as well as delving into any disparities in practice, which could be used to formulate pertinent research questions for the future.

Methods

A questionnaire was developed to target adult and paediatric endocrinologists who treat individuals with PWS. The survey comprised 4 parts focused on: (1) methods of substitution used, (2) appropriate age to initiate gonadal hormone replacement therapy (HRT), (3) dosing strategies, and (4) experience with the substitution treatment. Most questions were constructed as single answer binary or multiple-choice options. Free-text questions also allowed the experts to offer their own personal feedback on specific themes (see www.karger.com/doi/10.1159/000518342 for all online suppl. material).

The questionnaire was sent to participants in October 2019 in advance of the 10th IPWSO conference held in Havana, Cuba, in November 2019. Along with 98 attendees identified from the conference registration list, a further 30 IPWSO delegates who could not attend the conference received the survey for completion; the final respondent cohort represented physicians from 45 different countries. Ethics approval was not required because none of the protected patient information data were shared.

Data were manually extracted from the completed questionnaires of each participant. Furthermore, the country of the respon-

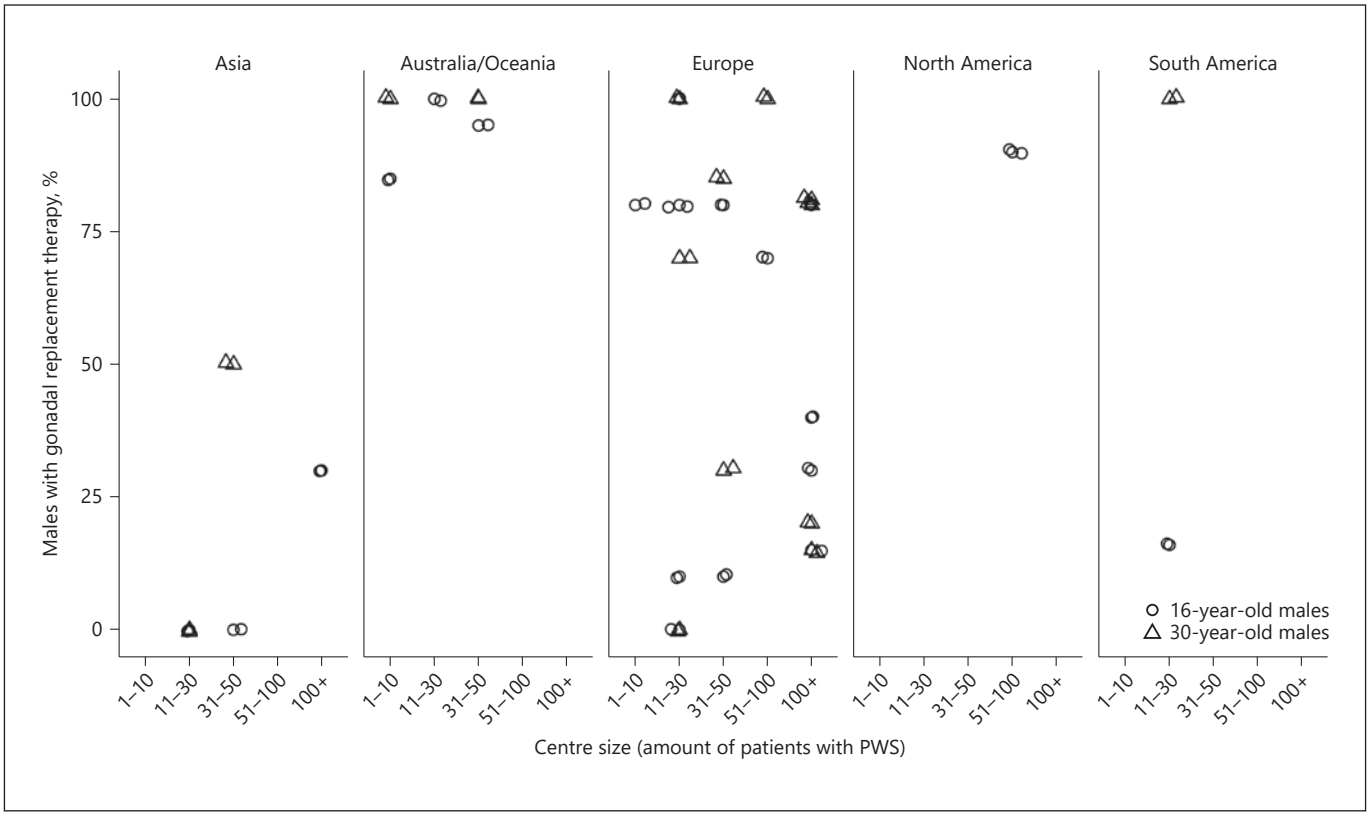

Fig. 1. Percentage of male PWS patients receiving gonadal hormone substitution by the centre size and region. PWS, Prader-Labhart-Willi syndrome.

dent was added, as well as the category of treated patients (paediatric or adult). Answers to free-text questions were coded using an inductive approach. Through an iterative process of reading, coding, discussing, rereading, and re-encoding, the answer categories to be used for evaluation were identified. Results of the questionnaire were presented at the IPWSO meeting in Cuba at a workshop.

Results

We received a total of 27 responses from 24 centres based in 19 countries (response rate: 21% for persons and 45% for countries). Reasons given for non-responding were not collected. Most responders are from European centres and the most common clinic size includes 11–30 PWS patients undergoing treatment, followed by centres with 100 or more patients (Table 1). Collectively, the total number of patients represented by the questionnaire responses is >1,000. Eighteen respondents work mainly with children and adolescents, 9 with primarily treated adults, and 2 smaller centres treat both younger and adult patients.

Males

Gonadal hormone substitution in males is prescribed by 24 of 26 physicians who responded to this section (not prescribing: centres in Bulgaria and Japan with both 11–30 adult patients); there was 1 missing answer from a USA participant with 100 + paediatric patients. There is a wide variation in the percentage of patients receiving gonadal hormone substitution for 16- and 30-year-old males (Fig. 1).

Dosing Strategies

The dosing strategy for male adults with PWS is heterogenous and ranges from 1 quarter to full replacement of the typical complete adult gonadal substitution dose. Differentiation by the centre size shows that smaller centres prefer to administer smaller doses (see online suppl. Table 1).

For adult patients, 12 of 24 respondents begin with low doses of testosterone described as either "1-quarter supplementation," "50–100 mg," "40–80 mg," or "50 mg" and increase their regimen slowly over time. The time intervals between both initial and subsequent dose in-

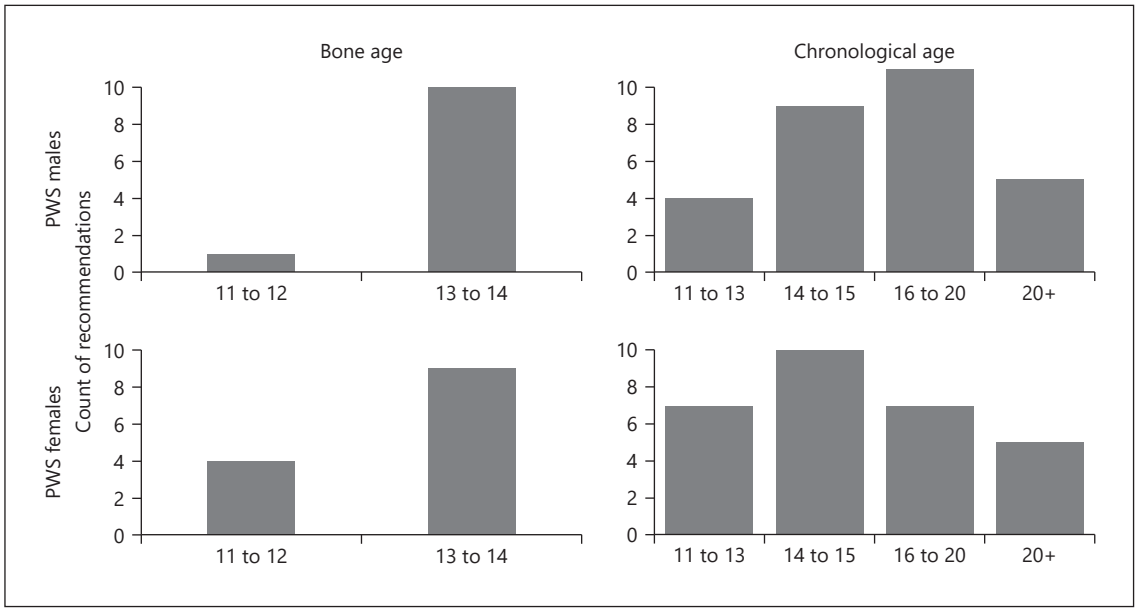

Fig. 2. Starting age recommendations for gonadal hormone substitution therapy in adolescents with PWS (multiple answers possible). PWS, Prader-Labhart-Willi syndrome.

creases are extremely diverse and categorised as: "after the first 3 months," "after the first 4–8 months," "every 6 months," and "every year". Final doses are usually not reached within <2 years. The dosage and progression in dosage are individualised (11 respondents) and based on various factors such as the behavioural response and laboratory values. Final doses were explicitly quantified as "120 mg," "200 mg," and "250 mg." One clinician always uses the same dose of 3 quarters of the supplementation dose in adults. A specific note by a single respondent on the application of testosterone gel in adults was made: "We start with 10 mg gel, which we increase by 10 mg every 4 weeks if there are no side effects, usually the final dose is 40–50 mg."

To induce puberty in adolescents with PWS, usually, from 1 quarter to 1 half of the regular dose for adolescents is used (online suppl. Table 2). There was a slight tendency for European clinicians to use smaller doses than their non-European colleagues. The preferred dose used by clinicians treating adolescents is more variable than the dose indicated by clinicians treating adults. A typical comment was noted: "Progression upward every 6 months for induction of puberty to near adult dosing that achieves testosterone levels within the lower 1/2 of the normal adult range. Sometimes slower increase in dose if family/caregivers are concerned about behavioural issues."

Best Starting Age for Gonadal Hormone Substitution

From 25 respondents who answered this question, most provided multiple answers. Eleven clinicians gave a bone age recommendation with all but one recommending a bone age of 13–14 years as the best starting age. The chronological age is recommended by 22 clinicians, roughly grouped into 2 categories of 14–15 years and 16–20 years (Fig. 2). Recommendations for initiating therapy at or over the age of 20 were made from non-European countries only (i.e., Australia, China, Japan, and USA). Clinicians treating mainly children and adolescents most often recommended chronological age ranges of 14–15 and 16–20 years as the best starting age (8 of 18 respondents), followed by a bone age of 13–14 years (7 of 18 respondents). There was no clear single age category identified by clinicians who primarily treat adults.

Other Starting Conditions

When making decisions on starting hormone substitution, the opinion of the family/patient/institutional caregiver is considered important by 18 clinicians as well as the behavioural status (15 respondents) and cognitive abilities of the patient (12 respondents). Also, pubertal arrest (2 respondents), the testosterone level (4 respondents), and bone mineral density (4 respondents) are further important factors to consider.

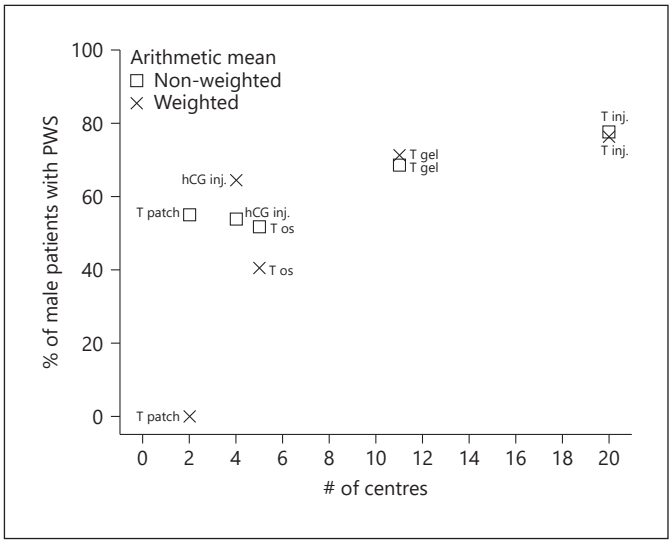

Fig. 3. Types of testosterone administration in males with PWS. Weighted arithmetic means were calculated using the centre size. T, testosterone; inj., injection; hCG, human chorionic gonadotropin; PWS, Prader-Labhart-Willi syndrome.

Type of Substitution Used

The preferred type of gonadal hormone substitution is testosterone administered intramuscularly (used by 20/23 centres with about 76% of their patients receiving this type of substitution). However, the use of testosterone in gel form is the second most common form of substitution (11/23 centres with about 70% receiving patients). The application of oral testosterone (5 centres, 40% patients) and human chorionic gonadotropin injections (4 centres, 64% patients) is less common. Testosterone patches are rarely used, and topical testosterone gel is more frequently used in European centres than non-European centres as well as more frequently in men than boys (Fig. 3; online suppl. Table 3).

Experiences with Gonadal Hormone Substitution Treatment

There were 21 respondents comprising 12 from European centres and 9 from non-European centres who provided feedback for this section of the survey. "Mainly good experiences" with gonadal HRT was noted by 9 of the 12 European centres but only 2 non-European sites.

Thirteen respondents (7 European and 6 non-European sites) experienced worsening or a new onset of behavioural problems associated with gonadal HRT in males. Six clinicians stated that there could be a dose dependency with testosterone and behavioural problems. One Japanese clinician stated that a small reduction in testosterone dose reduced aggressive behaviour, which was elicited by the (higher) starting dose. Four non-European, mainly paediatric centres in Brazil, New Zealand, USA, and Lithuania reported never having experienced behavioural problems in males with PWS during gonadal substitution treatment.

The reported side effects included acne and thromboembolism (1 respondent each). One clinician noted the positive effect of testosterone for the treatment of osteoporosis.

Contraindications for Gonadal Hormone Substitution

Possible contraindications for gonadal hormone substitution listed by the respondents were behavioural problems, heavily impaired cognitive abilities, and a negative opinion of the caregivers. Aggressive behaviour was the main cause for not offering or stopping therapy. Psychosis, as a rare event, was reported by 2 clinicians. Three respondents stated that gonadal hormone substitution was not considered for a patient if they had normal or at least detectable endogenous testosterone levels.

Females

Gonadal HRT in females is used by 25 of 26 respondents with one Japanese centre of 11–30 adult patients not providing any treatment whatsoever. A US centre of >100 paediatric patients did not respond to this section. In general, there is high variability in the percentage of patients receiving gonadal replacement therapy for 16- and 30-year-old females as well as within the geographical regions such as Europe (Fig. 4).

Dosing Strategies

For females without anticonception, most clinicians use 1 mg oestradiol per os per day (online suppl. Table 4). European centres tend to use lower doses than non-European centres. Administration of doses with patches is heterogeneous; the starting dose was described as 1/6 or 1/8 of a patch (overnight) with increases in the dose every 6 months. The dosing per patch varied considerably from 0.025 to 0.05 mg/day to 0.2 mg twice per week depending upon the preparation. Some respondents noted that they individualised the dosing for some cases relative to the patient's own oestradiol production. Seventeen of 20 respondents supplement oestradiol replacement with gestagen (progesterone) at some point over the course of treatment. Two paediatricians stated that they use oestradiol only during the initial stage of treat-

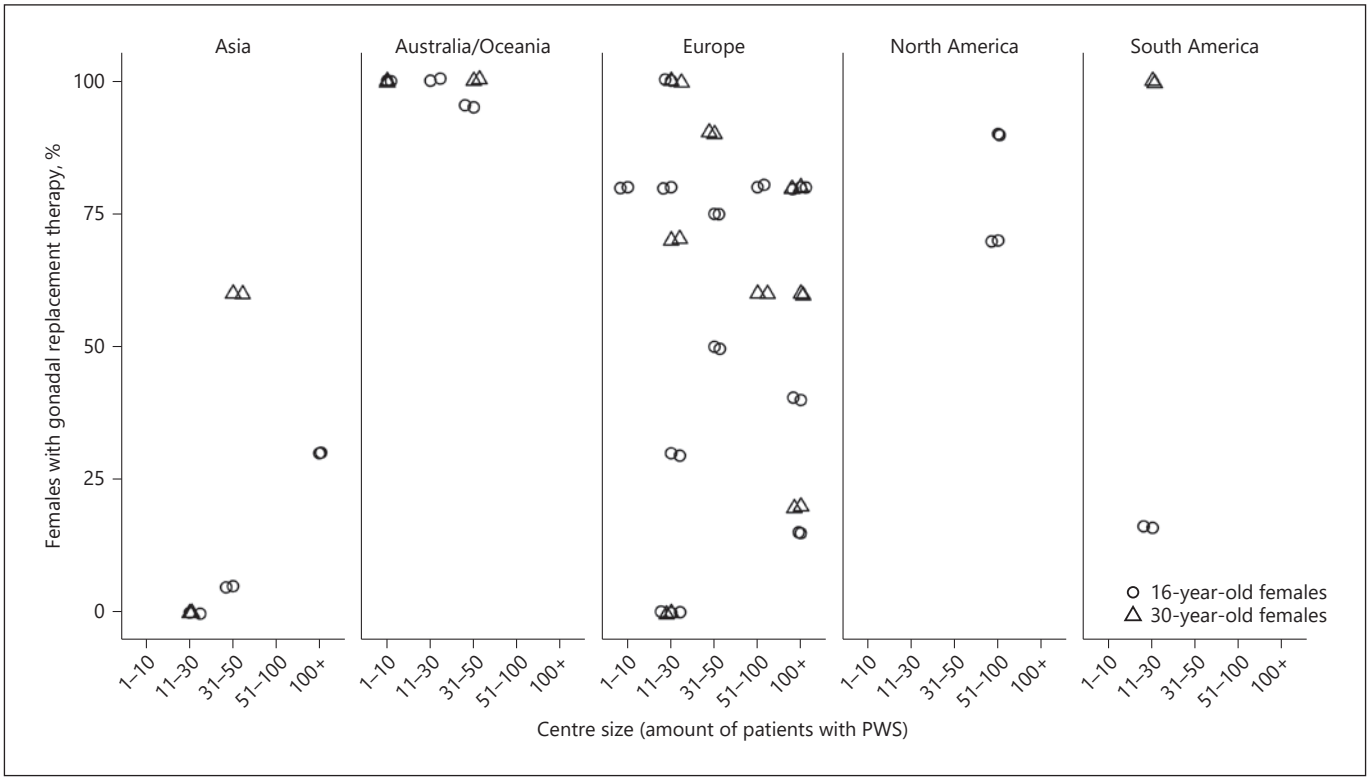

Fig. 4. Percentages of female PWS patients receiving gonadal hormone substitution therapy by the centre size and region. PWS, Prader-Labhart-Willi syndrome.

ment and add gestagen after 24 months or earlier in the case of vaginal bleeding. Three respondents do not use gestagen.

For females on anticonception medication, ethinylestradiol is usually combined with gestagen, and the preferred dose of ethinylestradiol is 0.03 mg (online suppl. Table 5). Dosing of oestradiol is higher in adult patients.

Best Starting Age for Gonadal Hormone Substitution

Of 23 respondents who answered this question, 13 use the bone age criterion with the majority recommending a bone age of 13–14 years as the best starting age. The chronological age is also used by 20 respondents with the recommendation to initiate treatment at 14–15 years of age (Fig. 2). Clinicians' mainly treating paediatric patients more often initiate therapy earlier than those primarily treating adults and use the criteria of either the bone age between 11 and 12 years or the chronological age between 11 and 13 years. Recommendations to delay treatment until 20 years of age or older were submitted by respondents from the non-European countries of Australia, China, Japan, and USA only.

Other Starting Conditions

The opinion of the family/patient/institutional caregiver was the most noted factor in the consideration of gonadal HRT for females by 21 clinicians. Other important factors include the behavioural status (15 respondents) or cognitive abilities of the patient (12 respondents), pubertal arrest (4 respondents), oestradiol level (4 respondents), and bone mineral density (3 respondents).

Type of Substitution Used

The overall preferred type of substitution and form of administration for females not on contraceptive medication is oral oestradiol and gestagen combined (23 centres, 77% of their patients) or oestradiol per os (10 centres, 61% of their patients), and this is dependent on age and the phase of induction or treatment (Fig. 5; online suppl. Table 6). The use of patches is also a quite common form of administration (oestradiol alone: 14 centres, 69% of patients; oestradiol and gestagen combined: 7 centres, 50% of patients). For females on anticonception medication, the use of the birth control pill is most popular. Intrauterine systems with hormones are used for these patients in only a few centres.

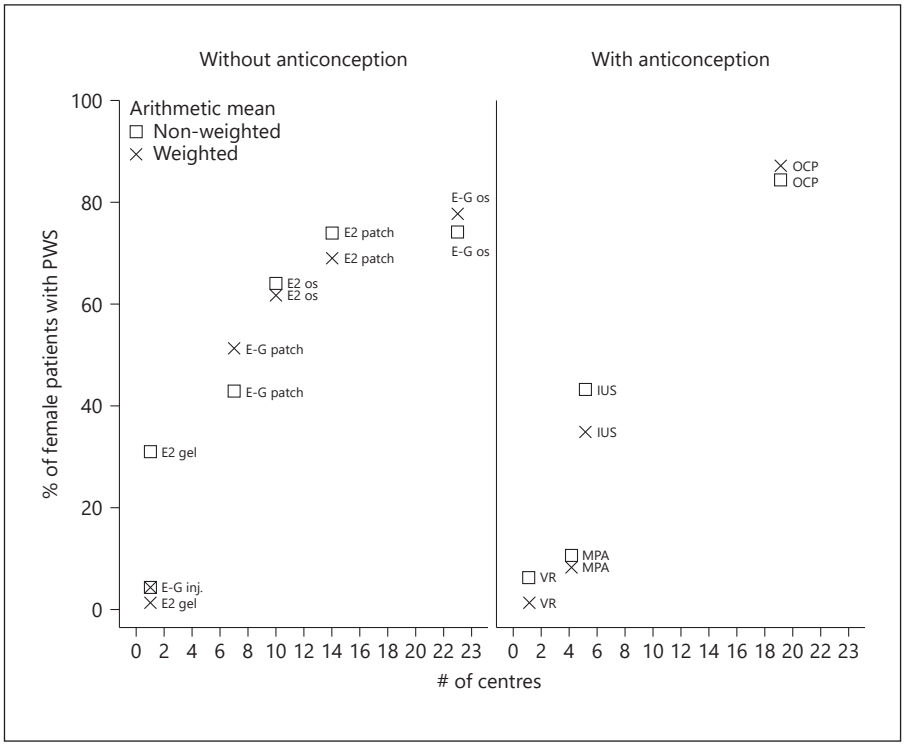

Fig. 5. Types of oestrogen administration in females with PWS. Weighted arithmetic means were calculated using the centre size. E2, oestradiol; E–G, oestradiol and gestagen; inj., injection; IUS, intrauterine system with hormones; MPA, medroxyprogesterone acetate; OCP, oral contraceptive pill; VR, vaginal ring; PWS, Prader-Labhart-Willi syndrome.

Experiences with Gonadal Hormone Substitution Treatment

Twelve of 19 respondents reported their mainly good experiences with gonadal hormone substitution in females with 7 clinicians explicitly stating that they have not observed any "worsening of mood" in their patients; 3 others did; however, reported negative mood effects. A dose-dependent effect of worsening behaviour is cautiously noted by 2 clinicians: "Most of the time this does not cause any problems. However, in some cases, the behavioural problems or psychosis worsens after the start of substitution, but this could be a coincidence." and "In one case, a possible connection with gonadal hormone substitution and psychosis." In comparison to their male patients, most clinicians' state: "I have not seen as many problems with mood complaints in females" and "Really better acceptance (of substitution) than in boys."

A range of side effects were reported. Four large and mainly European centres noted instances of associated psychosis. Four centres described menses-related hygiene problem, which is in line with a specific statement focused on the aspect that girls often prefer extended cycle regimens. Furthermore, there were 3 responses highlighting the side effect of thromboembolism with 1 physician who reported a 4% occurrence of venous thromboembolism and 1 case of pulmonary embolism in their large clinic. Last, there were single reports each of weight gain and hypertrichosis. Two clinicians noted the positive effect of gonadal substitution for the treatment of osteoporosis.

Contraindications for Gonadal Hormone Substitution

Classic contraindications for oestrogen substitution (e.g., thromboembolism, hypertension, and pre-existent cancer risk) were mentioned by 6 respondents. Severe obesity was also mentioned as a contraindication by 3 clinicians. Psychosis was mentioned only once as a contraindication. Although not specified as contraindications, behaviour, cognitive abilities, and caregiver opinion are also considered prior to making the decision to start treatment. Two respondents noted that when normal menstrual cycles are present, substitution is not indicated.

Discussion

While the questionnaire response rate was moderate, there were a substantial number of participating centres that treat a total number of at least 1,000 children and adults with PWS. Therefore, the survey results should provide adequate insight into the current treatment prac-

tice of hypogonadism in PWS, given the estimated prevalence of between 1:15,000 and 1:30,000 at birth for this rare genetic condition [13].

Almost all participants have experience in treating patients for hypogonadism, which reflects the high prevalence of hypogonadism in PWS [7, 12]. The percentage range of PWS children and adults being treated for hypogonadism (Fig. 1, 4) is large and suggests that there is no consensus on which patients should be treated. This aspect corresponds with the small number of studies on the treatment of hypogonadism in PWS that highlight the absence of clinical guidelines [12]. Nonetheless, there are clear reasons to supplement sex steroids in children and adults for assisting (further) biological and psychological development. One of the reasons for starting the induction of puberty is to maintain a normal height velocity. Further reasons for starting and maintaining sex steroid supplementation are to achieve complete sexual maturation [7], gain appropriate muscle mass [8], and maintain normal bone mineral density [12, 14–16].

The age at the start of induction differs significantly, and there are regional differences with non-European countries beginning at ages above 20 years in both males and females. From the survey, we could not deduce the reasons for these geographical differences in treatment protocols. We hypothesize that the differences could be due to the ambiguous symptoms of hypogonadism, foremost in girls, where the onset of puberty with breast development occurs at a normal age but further development is delayed [7]; hypogonadism is unmasked when menarche does not occur or is followed by oligomenorrhoea. In boys, the situation seems to be more obvious, where pubertal arrest occurs at an early age in most cases. Measurement of sex steroids can provide additional information. The fear of induction or aggravation of behavioural problems (e.g., problems in social interaction, aggressiveness, and irritability and rapid mood swings) due to gonadal substitution may be the reason for a delayed treatment of hypogonadism. However, the normal development of puberty with a strive for autonomy does take place in PWS and can be interpreted by less experienced parents as behavioural problems. Nowadays, growth hormone treatment is started at a fairly young age, and catch-up growth is usually accomplished in most children when they reach the pubertal age. Thus, final height should not be compromised by puberty induction at a normal age. From a biological point of view, induction of puberty could take place from the age of 11 years in girls and 13 years in boys, if pubertal progress stops. When we consider the status of intellectual disability and delayed psychological maturation, one might consider inducing at a later age. However, the question arises as to when children and adolescents with PWS will achieve the appropriate age of maturity to deal with the effects of inducing puberty. Overall, we therefore advocate the induction of puberty at the normal pubertal age, while taking into consideration that the starting age could be individualized based upon biological and psychological factors.

The administered dosage of sex steroids also widely differed although there was consensus on the gradual increase in dose over time like that for the treatment of isolated hypogonadism. Comments made regarding the gradual dosage increases reflect the cautiousness physicians have for creating or worsening behavioural problems, primarily in boys and men. The chosen adult dose of testosterone for men with PWS seems to be a little lower than the dose used for men with isolated hypogonadism. It is an important finding that most responders reported the treatment of hypogonadism and sex steroid supplementation in males and especially females and a lack of disturbances or behavioural problems in most cases. It is compelling that the larger centres seem more confident in using higher dosages possibly because of having made greater and positive clinical experiences. It might be that the emphasis placed on the effect of (mainly) testosterone amplifying pre-existent behavioural problems in PWS is overrated. Nevertheless, behavioural problems in PWS can be quite striking and one can appreciate any fears associated with disrupting a diligently built equilibrium between biology and behaviour. This aspect was highlighted by some of our colleagues and their few patients reported with psychosis as a possible result of sex hormone treatment. Yet, it is necessary to be aware that psychosis is a manifestation in adults with PWS that is not uncommon regardless of any treatment [17]. Overall, the results of this questionnaire point to the overall positive experiences with sex steroid supplementation in relation to behaviour, which should encourage us to further explore the physiological induction of puberty and sex steroid supplementation in PWS. It is also important to look at the decision-making process as it is both remarkable and reassuring to observe the importance placed on the opinion of parents and caregivers on starting sex steroid treatment. It is the responsibility of the treating physician to educate the family and caregivers who may be confronted with severe daily problems concerning behaviour yet might not have the ability or open-mindedness to weigh long-term goals of physical development and bone health against possible disruptions of stability within their everyday life at home. Honest and objective infor-

mation on the normal behavioural changes during puberty and the induction of puberty, which can be provided from the early years after diagnosis, could create an objective attitude towards this issue.

The type of substitution and mode of administration differs among centres. For boys and men, testosterone injections are mostly used followed by testosterone gel, which is a remarkable observation because gel administration requires proper daily application involving thorough hygiene measures to protect other people who live in the same household as the patient. From the responses, it is apparent that the care settings of males with PWS are capable of safely implementing this mode of treatment. The advantage of testosterone gel compared to depot injections could be the more stable serum levels achieved, which results in less mood swings in hypogonadal men [18]. For girls and women, it is difficult to obtain a clear picture of the current policies because the questionnaire did not clearly differentiate between the induction of puberty and long-term substitution. The fact that the onset of hypogonadism is more heterogeneous in girls possibly contributes to this finding. Nonetheless, the types of hormone substitution differ and are apparently based upon local experiences with treating hypogonadism and local availability of preparations. While oral preparations are mostly used for females, patches are also popular, and this trend is similar to the experiences observed for Turner syndrome patients [19]. Fertility control is an important topic for adolescent girls and women with PWS, as is shown in the reported treatment possibilities. This outcome confirms the few reports focused on fertility in girls and women with PWS [20].

Classic contraindications for supplementation with oestrogens (e.g., thromboembolism, hypertension, and pre-existent cancer risk) were commonly mentioned as reasons to withhold hormone supplementation in females. However, HRT with oestradiol, as is commonly used in PWS, has a different safety profile to alkyl-oestradiol that is the active ingredient in contraceptive pills. There is a beneficial effect on cardiovascular function (e.g., hypertension), and epidemiological and basic science studies do not support the concerns that HRT with 17-beta-oestradiol increases the risk of thrombosis [21]. Additionally, one could argue that the goal of HRT in PWS is to simply normalise the serum levels of sex steroids through supplementation, and consequently, the risks for thromboembolic events and breast cancer are also "normalised" to physiological levels.

Although the worldwide representation of this study was good (24 centres and >1,000 patients), the study has its limitations. First, the survey questions were apparently not always straightforward and clear and could be interpreted in multiple ways. Second, the coding of the answers was not always possible without interpretation. We tried to prevent bias by discussing these findings within our team. Third, there could be a selection bias in the results as European centres were overrepresented compared to non-European centres.

Overall, it was still possible to extract conclusions from the current questionnaire on the treatment of hypogonadism in PWS. It is clear that given the high prevalence of hypogonadism in PWS, experience with treatment is present and growing. There is no consensus on who to treat or at what age to start treatment and some colleagues treat all their patients, and others treat boys and girls at early pubertal ages. Treating hypogonadism in people with PWS is apparently feasible and even at a normal pubertal age. The experiences highlighting the lack of behavioural disturbances in males and especially, females with PWS during sex steroid supplementation is an important and reassuring finding. Using lower dosages, especially for males because of the possible induction of behavioural problems and fears associated with this issue, could potentially provide suboptimal care for our patients and this practice should be carefully studied. The types and application modes of sex steroids are quite diverse and seem to result from local experiences and availability. These diverse experiences could provide us with information about the effects of the varying methods on clinical and patient-reported outcomes.

Which questions must be solved over the next years? Apparently, we lack consensus on who to treat, when to start treatment, how to monitor the effects of treatment, and lack data on the long-term follow-up after treatment of hypogonadism in PWS. Clearly, there is knowledge and experience in the field and consequently, a consensus statement from IPWSO would be a primary goal. The recent review paper on hypogonadism in PWS with recommendations for diagnosis, treatment, and follow-up [12] could be used as a starting point for achieving this main aim. The review authors also suggest developing an instrument for monitoring behaviour in people with PWS. This will hopefully lead to multicentre randomization of treatment to allow appropriate comparisons of the therapy protocols.

Acknowledgments

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Statement of Ethics

This retrospective review of patient data did not require ethical approval in accordance with local/national guidelines. Written informed consent from participants was not required in accordance with local/national guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

U.E. and C.F. contributed to conceptualization; A.S. contributed to methodology; A.S. software; A.S., C.F., and C.K. contributed to validation; A.S. contributed to formal analysis; A.S. and U.E. contributed to investigation; C.F. contributed to resources; A.S. contributed to data curation; C.N. contributed to writing – original draft preparation; C.N., A.S., U.E., and C.K. contributed to writing – review and editing; A.S. contributed to visualization; U.E. contributed to supervision; C.F. contributed to project administration. All the authors have read and agreed to the published version of the manuscript.

Data Availability Statement

The data that support the findings of this study are not publicly available but are available from the corresponding author (U.E.) upon request.

References

1 Prader A, Labhart A, Willi H. Ein Syndrom von Adipositas, Kleinwuchs, Kryptorchismus und Oligophrenie nach myotonieartigem Zustand im Neugeborenenalter. Schweiz Med Wochenschr. 1956;86:1260–1.
2 Holm VA, Cassidy SB, Butler MG, Hanchett JM, Greenswag LR, Whitman BY, et al. Prader-Willi syndrome: consensus diagnostic criteria. Pediatrics. 1993;91(2):398–402.
3 Goldstone AP, Holland AJ, Hauffa BP, Hokken-Koelega AC, Tauber M. Speakers contributors at the second expert meeting of the comprehensive care of patients with PWS. Recommendations for the diagnosis and management of Prader-Willi syndrome. J Clin Endocrinol Metab. 2008;93(11):4183–97.
4 Eiholzer U, l'Allemand D. Growth hormone normalises height, prediction of final height and hand length in children with Prader-Willi syndrome after 4 years of therapy. Horm Res. 2000;53(4):185–92.
5 Eiholzer U, Nordmann Y, l'Allemand D, Schlumpf M, Schmid S, Kromeyer-Hauschild K. Improving body composition and physical activity in Prader-Willi Syndrome. J Pediatr. 2003;142(1):73–8.
6 Eiholzer U, l'Allemand D, Rousson V, Schlumpf M, Gasser T, Girard J, et al. Hypothalamic and gonadal components of hypogonadism in boys with Prader-Labhart- Willi syndrome. J Clin Endocrinol Metab. 2006;91(3):892–8.
7 Hirsch HJ, Eldar-Geva T, Bennaroch F, Pollak Y, Gross-Tsur V. Sexual dichotomy of gonadal function in Prader-Willi syndrome from early infancy through the fourth decade. Hum Reprod. 2015;30(11):2587–96.
8 Eiholzer U, Grieser J, Schlumpf M, l'Allemand D. Clinical effects of treatment for hypogonadism in male adolescents with Prader-Labhart-Willi syndrome. Horm Res. 2007;68(4):178–84.
9 Kido Y, Sakazume S, Abe Y, Oto Y, Itabashi H, Shiraishi M, et al. Testosterone replacement therapy to improve secondary sexual characteristics and body composition without adverse behavioral problems in adult male patients with Prader-Willi syndrome: an observational study. Am J Med Genet A. 2013;161A(9):2167–73.
10 Heksch R, Kamboj M, Anglin K, Obrynba K. Review of Prader-Willi syndrome: the endocrine approach. Transl Pediatr. 2017;6(4):274–85.
11 Bakker NE, Kuppens RJ, Siemensma EP, Tummers-de Lind van Wijngaarden RF, Festen DA, Bindels-de Heus GC, et al. Bone mineral density in children and adolescents with Prader-Willi syndrome: a longitudinal study during puberty and 9 years of growth hormone treatment. J Clin Endocrinol Metab. 2015;100(4):1609–18.
12 Noordam C, Höybye C, Eiholzer U. Prader-Willi syndrome and hypogonadism: a review article. Int J Mol Sci. 2021;22(5):2705.
13 Orphanet. The portal for rare diseases and orphan drugs; 2021 Apr 21. Available from: https: //www.orpha.net/consor/cgi-bin/Disease_Search.php?lng=EN&data_id=139.
14 Donze SH, Kuppens RJ, Bakker NE, van Alfen-van der Velden JAEM, Hokken-Koelega ACS. Bone mineral density in young adults with Prader-Willi syndrome: a randomized, placebo-controlled, crossover GH trial. Clin Endocrinol. 2018;88(6):806–12.
15 Butler JV, Whittington JE, Holland AJ, Boer H, Clarke D, Webb T. Prevalence of, and risk factors for, physical ill-health in people with Prader-Willi syndrome: a population-based study. Dev Med Child Neurol. 2002;44(4):248–55.
16 Kroonen LT, Herman M, Pizzutillo PD, Macewen GD. Prader-Willi syndrome: clinical concerns for the orthopaedic surgeon. J Pediatr Orthop. 2006;26(5):673–9.
17 Whittington J, Holland A. A review of psychiatric conceptions of mental and behavioural disorders in Prader-Willi syndrome. Neurosci Biobehav Rev. 2018;95:396–405.
18 Lakshman KM, Basaria S. Safety and efficacy of testosterone gel in the treatment of male hypogonadism. Clin Interv Aging. 2009;4:397–412.
19 Donaldson M, Kriström B, Ankarberg-Lindgren C, Verlinde S, van Alfen-van der Velden J, Gawlik A, et al. Optimal pubertal induction in girls with turner syndrome using either oral or transdermal estradiol: a proposed modern strategy. Horm Res Paediatr. 2019;91(3):153–63.
20 Gross-Tsur V, Hirsch HJ, Benarroch F, Eldar-Geva T. The FSH-inhibin axis in Prader-Willi syndrome: heterogeneity of gonadal dysfunction. Reprod Biol Endocrinol. 2012;10:39.
21 Hartmann BW, Huber JC. The mythology of hormone replacement therapy. Br J Obstet Gynaecol. 1997;104(2):163–8.