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Availability, Usage, and Preferences of Estradiol and Progestogen Preparations for Puberty Induction from a Multicentral Perspective

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Keywords
Puberty induction · Availability · Oestrogens · Progesterone · Hormone replacement therapy · Hypogonadism · Turner syndrome

Abstract
Introduction: Natural oestrogen administration as oral or transdermal 17β-estradiol is recommended for pubertal induction in girls with hypogonadism. However, suitable low-dose formulations are not consistently available globally. This questionnaire study aimed to identify the current availability of oestrogen and progesterone preparations worldwide. ***Methods:*** Endorsed by the ESPE Turner Syndrome Working Group, the questionnaire targeted paediatric endocrinologists. Questions focused on accessibility of oral/transdermal 17β-estradiol and progestogen preparations. Responses were collected through a SurveyMonkey survey disseminated via ESPE channels, direct outreach, and conferences from June 2020 to December 2022. ***Results:*** Participation included 229 healthcare professionals from 45 countries. Oral and transdermal 17β-estradiol in adult dosage was highly accessible (86.5% and 84.3%), with transdermal administration the preferred form (62.8%). Most commonly available estradiol preparations included 50 μg patches (32 countries) and 1 or 2 mg tablets (65.8% and 71.1% countries). However, 0.5 mg 17β-estradiol tablets were available in only 20% of respondents from 8 countries.

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Patches delivering 14 or 25 μg/day of 17β-estradiol were available in 3 and 20 countries, respectively. Oral progestogen had widespread availability (96.0%) and preference (87.0%), while transdermal usage was limited to 15.2% of respondents. ***Conclusion:*** This study highlights global challenges in accessing suitable hormone preparations for female pubertal induction. In most countries, the lowest dose of the estradiol is 50 μg for patches and 2 mg for tablets. Appropriate low-dose 17β-estradiol tablets are much less available than low-dose patches. Our survey underscores the importance of adapting guidelines to local availability, and the need for improved accessibility to address these global disparities.

Table 1. Distribution of profession among the 229 respondents to a questionnaire on the availability and usage of oestrogen and progestogen preparations in different countries

Profession	Respondents, *n* (%)
Paediatric endocrinologist	199 (86.90)
Adult endocrinologist	23 (10.04)
Paediatrician with an interest in endocrinology	13 (5.68)
Trainee in adult/paediatric endocrinology	4 (1.75)
Nurse practitioner	0 (0)
Other	6 (2.62)
"Gynaecologist"	4 (1.75)
"Paediatric diabetician"	1 (0.44)
"TS patient-physician"	1 (0.44)

Introduction

Hypogonadism in female patients may be caused by decreased levels of gonadotropins (hypogonadotropic hypogonadism) or by structural changes in the ovaries leading to primary ovarian insufficiency (hypergonadotropic hypogonadism). In both cases, the clinical manifestation includes delayed or absent puberty. Treatment typically involves pubertal induction with oestrogens and introduction of progesterone towards the end of the induction period [1]. The most common cause of hypogonadism requiring hormone replacement therapy is Turner syndrome with progressive ovarian failure due to accelerated atresia of the oocytes [2–5].

Recent papers including British guidelines [6], Endo-ERN [7], and the international Cincinnati guidelines [8] recommend use of natural rather than synthetic oestrogens in the form of 17β-estradiol. Oestrogen may be given orally using tablets or by applying patches or gel to the skin – the transdermal method. The most effective and safe method of administration has not yet been determined. To mimic natural pubertal progress, there is a need of a gradual increment of oestrogen over a span of 2–3 years until reaching an adult dosage. To commence pubertal induction using E2 patches administered nocturnally, initial oestrogen doses may range from 0.05 to 0.07 μg/kg. Alternatively, oral oestradiol therapy is recommended to be administered at a fixed dose, e.g., 0.2 mg/day in the initial year and 0.5 mg/day in the subsequent year. Progesterone should be added at least after 2 years of treatment or after the onset of menstrual bleeding [7].

Compliance with the recent guidelines depends on the availability of suitable oral and transdermal preparations, but preliminary enquiries reveal that the availability of suitable low-dose formulations of 17β-estradiol is a problem in many countries. The purpose of this questionnaire study, therefore, was to establish which oestrogen and progesterone preparations are currently available in the countries of healthcare workers who are experts in paediatric endocrinology and/or members of societies for paediatric endocrinology (e.g., ESPE, PES).

Methods

An English version of a questionnaire on the availability of oral/transdermal 17β-estradiol and progestogen preparations was prepared with support from the Steering Committee of the ESPE Turner Syndrome Working Group (TSWG) and in consultation with the wider membership of the group. The questionnaire dedicated to healthcare professionals (HCPs) consisted of two parts (a and b). All components of the questionnaire were converted into a survey in *SurveyMonkey* (https://www.surveymonkey.com/). Parts HCP a and b consisted of 14 (Q1–Q14/general) and 5 (Q15–Q19/details regarding specific preparations) questions, respectively. In 9 (Q7, Q8, Q11, Q12, Q15, Q16, Q17, Q18, and Q19) of the 19 questions, respondents had the possibility of indicating more than one answer, and for most questions participants were able to choose "Other" and specify their responses by a descriptive answer.

The complete version of the questionnaires used in this study is available as an online supplementary file (for all online suppl. material, see https://doi.org/10.1159/000539236). Questionnaire HCP a and b (https://www.surveymonkey.com/r/TNF3VXT) concerning the availability of preparations/doses in specific countries/centres and preferred products were sent directly to colleagues from ESPE as well as to other colleagues with known expertise and interest in the field of pubertal induction. Furthermore, both parts of the questionnaire were disseminated via a link through the ESPE "Newsletter" and/or "News Alert Service" to all ESPE members, reaching over 1,200 members from over 90 countries. ESPE delegates were encouraged to take part during the

Country	*Respondents n (%)*
Germany (2,4)	29 (12.6 %)
Italy (2,3,4)	27 (11.79%)
United Kingdom of Great Britain and Northern Ireland (2,3,4)	23 (10.04%)
Poland (1,2,3,4)	19 (8.30%)
United States of America (1,2,3,4)	15 (6.55%)
Netherlands (3,4)	13 (5.68%)
Switzerland (2,4)	12 (5.24%)
Belgium (2,4)	9 (3.93%)
Austria (2,4), France (2,4)	7 (3.06%) in each country
Sweden, Turkey (2)	6 (2.62%) in each country
Denmark (2,4), Romania (2,4)	5 (2.18%) in each country
Greece (4), Israel, Singapore (2,4)	3 (1.31%) in each country
Albania[UMI] (1,3), Algieria (3,4)[LMI], Bulgaria[UMI] (4), Czech Republic (2), Estonia, Finland (2), Hungary (4), India[LMI] (4), Lithuania (4)	2 (0.87%) in each country
Brazil[UMI] (2,4), Canada (2,3), Cyprus (4), Egypt[LMI], Georgia[UMI], Iceland (2), Ireland (2,4), Japan, Latvia (4), Luxembourg (4), Mexico[UMI], New Zealand, Oman, Serbia[UMI] (4), Slovakia, Slovenia, Spain (2), Sri Lanka[LMI], North Macedonia[UMI] (4)	1 (0.44%) in each country

Fig. 1. Country distribution among the 229 respondents from 45 countries. LMI and UMI countries, classified according to World Bank Country and Lending criteria, are shown with superscript. The numbers in parentheses indicate the countries in which preparations with the lowest doses of oestradiol as 14 µg patches (1), 2–25 µg patches (2), 0.5 mg tablets (3), and micronized progesterone in tablets (4) are available.

TSWG session at the annual ESPE conference. The time frame for receiving feedback was from June 2020 until the end of 2022.

The questionnaire responses were reviewed by the TSWG Steering Committee Members. A teleconference was organized to review the data and draw conclusions. Where applicable, countries within and outside Europe were classified according to the World Bank Atlas method as lower middle income (LMI) when gross national income per capita was between USD 1,036 and USD 4,085, and as upper middle income (UMI) when gross national income was between USD 4,086 and USD 12,615 [9].

Results

A total of 229 HCPs from 45 countries confirmed their agreement to anonymous participation and took part in this survey. The respondents' countries and professions (Q2, Q4) are presented in Table 1. This shows that most respondents (86.9%) were paediatric endocrinologists, followed by adult endocrinologists (10%). Figure 1 demonstrates the distribution of responders from different countries, with LMI and

Table 2. Available oestrogen preparations

Answer choices	Respondents, *n*	Respondents, %	Countries, *n*	Countries, %
Transdermal 17 beta-E2 (177 respondents, 41 countries)				
Climara® 50	52	29.4	14	34.1
Estraderm MX® 25	46	26.0	7	17.1
Estraderm MX® 50	43	24.3	8	19.5
Dermestril 50®	40	22.6	8	19.5
Estradot® 50	38	21.5	15	36.6
Climara® 100	35	19.8	10	24.4
Estraderm MX® 100	34	19.2	8	19.5
Systen 50®	33	18.6	7	17.1
Estradot® 75	32	18.1	11	26.8
Estragel® 0.06%	32	18.1	13	31.7
Estradot® 100	30	16.9	12	29.3
Estradot® 37.5	29	16.4	11	26.8
Climara® 25	28	15.8	10	24.4
Estraderm® 50 (reservoir!)	28	15.8	13	31.7
Vivelle® 50	27	15.3	7	17.1
Climara® 75	27	15.3	9	21.9
Estraderm® 25 (reservoir!)	27	15.3	11	26.8
Evorel® 50	27	15.3	10	24.4
Vivelle® 25	25	14.1	6	14.6
Vivelle® 37.5	25	14.1	6	14.6
Vivelle® 75	24	13.6	6	14.6
Vivelle® 100	24	13.6	6	14.6
Evorel® 25	24	13.6	7	17.1
Climara® 37.5	23	13.0	8	19.5
Divigel® 0.1%	20	11.3	7	17.1
Estraderm® 100 (reservoir!)	19	10.7	10	24.4
Evorel® 100	17	9.6	8	19.5
Evorel® 75	16	9.0	6	14.6
Menostar® 14	12	6.8	3	7.3
Oesclim® 50	11	6.2	3	7.3
Oesclim® 25	9	5.1	2	4.9
None	6	3.4	5	12.2
Other	61	34.5	25	61.0
Oral 17 beta-E2 (145 respondents, 38 countries)				
Estrofem® 2 mg	81	55.9	25	65.8
Estrofem mite® 1 mg	60	41.4	21	55.3
Estrace® 1 mg	20	13.8	6	15.8
Zumenon®/Oromone® 1 mg	19	13.1	5	13.2
Estrace® 0.5 mg	18	12.4	6	15.8
Estrace® 2 mg	17	11.7	5	13.2
Cetura® 0.5 mg	11	7.6	2	5.3
None	7	4.8	7	18.4
Other	37	25.5	16	42.1
Oral estradiol valerate (152 respondents, 38 countries)				
Progynova® 2 mg	108	71.05	24	63.2
Progynova® 1 mg	96	63.16	23	60.5
Climaval® 1 mg	12	7.89	4	10.5
Climaval® 2 mg	7	4.61	4	10.5
None	10	6.6	9	23.7
Other	22	14.5	8	57.9

Table 2 (continued)

Answer choices	Respondents, *n*	Respondents, %	Countries, *n*	Countries, %
Oral ethinylestradiol (121 respondents, 36 countries)				
Ethinylestradiol 2 μg tablets, UCB Pharma Ltd	53	43.80	20	55.5
Ethinylestradiol 10 μg tablets, UCB Pharma Ltd	36	29.75	13	36.1
None	13	10.7	10	27.8
Other	45	37.2	16	44.4

Responses are ranked from the most frequent to the least frequent.

Table 3. Natural (17β-estradiol) doses available

Answer choices	Respondents, *n*	Respondents, %	Countries, *n*	Countries, %
Transdermal E2 (177 respondents, 41 countries)				
Patches 14 μg	12	6.8	3	7.3
Patches 25 μg	90	51.0	20	48.8
Patches 37.5 μg	57	32.2	17	41.5
Patches 50 μg	143	80.8	32	78.0
Patches 75 μg	67	37.9	18	43.9
Patches 100 μg	88	49.7	21	51.2
Gel 0.06%	32	18.1	13	31.7
Gel 0.1%	20	11.3	7	17.1
None	6	3.4	5	12.2
Oral 17 beta-E2 (145 respondents, 38 countries)				
0.5 mg	29	20.0	8	21.1
1 mg	88	60.7	25	65.8
2 mg	95	65.5	27	71.1
None	7	4.8	7	18.4
Oral estradiol valerate (152 respondents, 38 countries)				
1 mg	101	66.4	25	65.8
2 mg	111	73.0	24	63.2
None	10	6.6	9	23.7

UMI countries marked with superscript. Figure 1 also indicates the availability of low-dose estradiol preparations, with 14 μg patches (n = 3), 25 μg patches (n = 20), 0.5 mg tablets (n = 8), and micronized progesterone tablets (n = 26) given in parentheses as 1, 2, 3, and 4, respectively.

Respondents were from 31 countries within Europe (including five UMI countries) and 14 from outside Europe (including three LMI and three UMI countries). There was considerable variability in the number of respondents from different countries with 12–29 respondents/country in seven countries, 4–9 in seven countries, and 1–3 in the remaining 31 countries (including all three LMI and all eight UMI countries).

Time (Age and Duration) of Puberty Induction (Q5, Q6)

A total of 117/223 (52.5%) participants stated that they recommended starting oestrogen therapy between the ages of 10 and 12 years, while 79/223 (35.4%) recommended starting between 12 and 14 years. The "Other" option was chosen by 22/223 (9.9%) of respondents, whose specified responses indicated that they based their decisions about oestrogen therapy on their patients' height, bone age, gonadotropin levels, and situation regarding growth hormone therapy. When asked about the time scale for gradual incremental doses of oestrogen between starting induction and reaching adult dose 142/

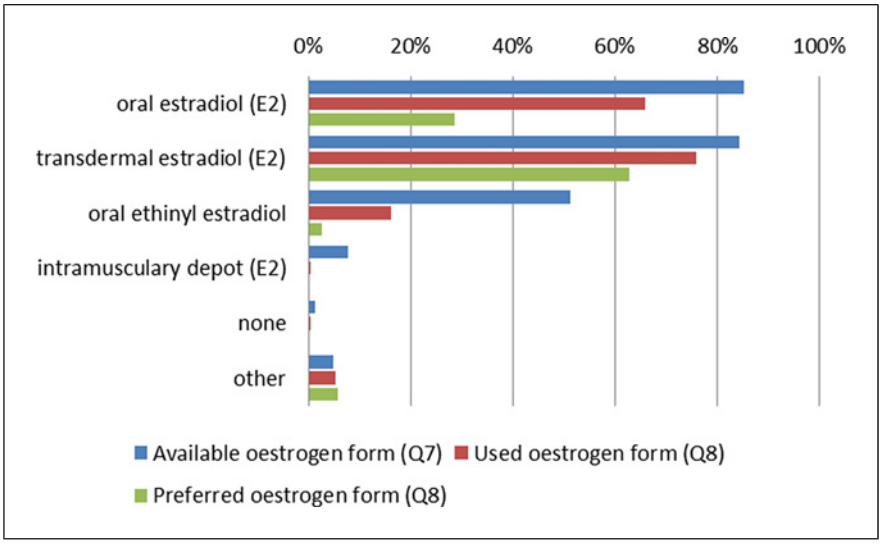

Fig. 2. Chart showing the availability (Q7), used (Q8), and preferred (Q9) oestrogen forms for pubertal induction.

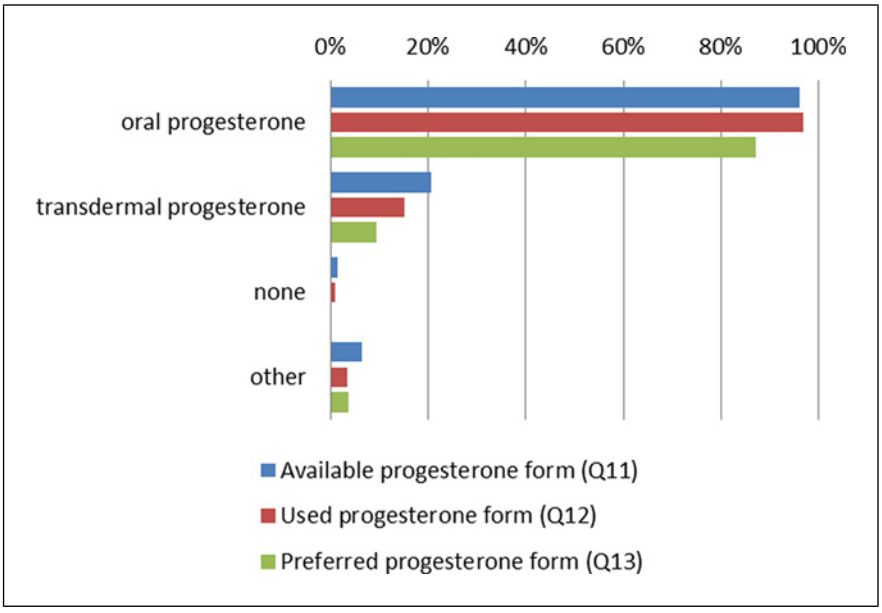

Fig. 3. Chart showing available (Q11), used (Q12), and preferred (Q13) progestogen forms for pubertal induction.

223 (63.7%), respondents reported a pubertal induction period of 2–3 years in their centres, while 42/223 (18.8%) professionals reported 3–4 years and 24/223 (10.8%) only 1–2 years.

Oestrogen Preparation/Availability (Q7), Usage (Q8), and Preferences (Q9 and 10)

Oral and transdermal forms of bioidentical human oestrogens (estradiol/17β-estradiol/E2) were the most frequently reported available oestrogen forms with 193/223 (86.5%) and 188/223 (84.3%) respondents reporting on the availability of these, respectively. Other indicated options of oestrogen therapy were oral ethinylestradiol (114/223 answers – 51.1%) and intramuscular depot injection (17/223 answers – 7.6%). By specifying the response "Other," professionals proposed two other available options accessible for their patients – oral estradiol valerate and estradiol gel.

Transdermal estradiol/patch (E2) was the most frequently used form of oestrogen – chosen by 160/211 (75.8%) specialists. Oral E2 form was used by 144/211 (68.2%) professionals, with oral ethinylestradiol being

Table 4. Available progestogen preparations

Answer choices	Respondents (total = 185), *n*	Respondents, %	Countries (total = 42), *n*	Countries, %
Duphaston® (dydrogesterone) 10 mg	128	69.2	26	61.9
Provera® (medroxyprogesterone acetate) 5 mg	107	57.8	25	59.5
Provera® (medroxyprogesterone acetate) 10 mg	103	55.7	24	57.1
Utrogestan® (micronized progesterone) 100 mg	71	38.4	25	59.5
Luteina® (progesterone s.l.) 50 mg	16	8.7	3	7.14
Progesterone Besins® (micronized progesterone) 100 mg	13	7.0	5	11.9
Progesterone Besins® (micronized progesterone) 200 mg	10	5.4	4	9.5
Luttagen® (progesterone) 100 mg	5	2.7	3	7.1
Luttagen® (progesterone) 200 mg	5	2.7	3	7.1

Responses ranked from the most frequent to the least frequent.

chosen by 34/211 (16.1%) respondents. Among "Other," respondents entered estradiol gel and oral conjugated oestrogens. However when asked about their preferred oestrogen form, the majority (140/223 respondents, 62.8%) chose transdermal estradiol (E2), with oral estradiol chosen by 64/223 (28.70%) professionals.

Results related to availability of oestrogen preparations (Q15–18), doses, and forms are presented in Table 2 which shows all the available oestrogen preparations, in Table 3 which indicates the available doses of "natural" or 17β-estradiol, and in Figure 2 which shows the questionnaire responses to items 7, 8, and 9 concerning availability, use, and preference for oestrogen preparations. The availability in individual countries of the lowest oestrogen doses is marked in Figure 1 as mentioned earlier.

It can be seen from Figure 1 and Table 3 that oestrogen patches delivering 14 μg/day of 17β-estradiol were available in only three countries (12 respondents), while patches delivering 25 μg/day were available in 20 countries (90 respondents). Also, 0.5 mg tablets of 17β-estradiol were available in only 8 countries (29 respondents). Figure 2 shows that although ethinyl estradiol ranked low as a preferred oestrogen form, it was nevertheless used by 15% of responders.

Progestogen Form/Availability (Q11), Usage (Q12), and Preferences (Q13)

When asked about progestogen replacement therapy, oral progestogen was the most frequently mentioned route of delivery: in terms of availability (214/223, with 96.0% of responses), use (204/211, with 97% of responses), and preference (194/223, with 87.0% of responses). A transdermal form was available for 46/223 (20.6%) professionals, while 32/211 (15.2%) declared using it in their centres. However, only 21/223 (9.4%) respondents preferred this option over the oral form.

Results related to Q11, Q12, and Q13 and availability of progestogen preparations (Q19) are presented in Figure 3 and Table 4. Figure 1 shows that micronized progesterone tablets were available in 26 of the 45 countries.

Discussion

While the process of pubertal induction in girls with hypogonadism should be based on the same fundamental principles, guidelines should be adapted to take into account local availability of preparations. This research has provided us with insight into the practices used by professionals from different parts of the world.

According to this study, specialists have a preference for utilizing natural forms of estradiol, in alignment with current guidelines which suggest the benefits of natural over synthetic oestrogens [6–8, 10]. The survey shows that transdermal forms of estradiol are favoured over oral preparations. One possible explanation for such preferences is the limited availability of low-dose estradiol tablets. However, we cannot be certain on this point since the reason for the respondents' preference was not asked.

The smallest tablet of 17β-estradiol is 0.5 mg; however, only one-fifth of respondents, from 8 countries, confirmed the availability of this preparation. Of note, "availability" refers to the clinician being able to order 0.5 mg tablets through their pharmacy, but this will usually mean importing from abroad since the only countries which actually manufacture 0.5 mg tablets are the Netherlands and the USA. Patches delivering 14 or

25 μg/day of 17β-estradiol were available on the market in only 3 and 20 countries, respectively.

There is currently no published randomized research comparing the effectiveness and safety of oral and transdermal routes. Therefore, the decision on the route of administration is based on the physician's experience, patient and parental personal preferences, as well as the current availability and cost of the medication. In 2019, the ESPE TSWG put forth a novel strategy, which involves achieving a consensus regarding both oral and transdermal protocols while concurrently undertaking a prospective observational study aimed at comparing the outcomes resulting from these two treatment regimens [11]. Regarding recommended doses for inducing puberty in adolescents, it is worth noting that such doses are not readily available. As indicated in Table 4, the most commonly available estradiol preparations come in the form of 50 μg patches and 1 or 2 mg tablets. Unfortunately, therefore, there are currently no preparations on the market containing estradiol doses suitable for puberty induction. This situation often leads to the utilization of off-label formulations intended for adults and custom doses prepared by parents or pharmacies [12]. A study conducted by Ankarberg-Lindgren et al. [13] found that Systen, Estraderm MX, and Oesclim patches can be safely shared and stored in their original protective pouches for up to 1 month at +35°C. However, some patches were too small to be properly cut into low doses and are not stable in elevated temperatures. It is important to note that other accessible transdermal preparations like gels or sprays are not recommended for puberty induction since there is no way to deliver the minimal doses required, using these formulations.

From our observations in this study, we have noticed that specialists have varying approaches regarding the timing and duration of pubertal induction. According to guidelines, oestrogen therapy should commence at the age of 11–12 years, with the dose gradually increasing over a period of 2–3 years to emulate the natural process [7]. However, only half of our respondents mentioned this recommended age range, and less than two-third of specialists adhered to the recommended duration for puberty induction. When studying open answers selected as "Other," we observed that these differences may be attributable to the fear of accelerating bone age, which could lead to an unsatisfactory final height.

There were no controversies regarding the route of progestogen supplementation. Most of the respondents preferred the oral formulations, and these forms were also widely accessible. Micronized progesterone, recognized as the best form used during puberty induction [14, 15], was available in 26 countries.

To our knowledge, there is only one study similar to ours. Deeb et al.'s [16] survey, published in 2022, addressed the availability and access to oestrogen preparations for pubertal induction and maintenance in girls with hypogonadism in the Middle East. The answers of 99 physicians from 16 countries showed that the most commonly available oestrogens were conjugated oestrogens (29.3%), ethinylestradiol preparations (26.3%), and combined oral contraceptive pills (32.3%). Oral and transdermal 17-β estradiol was available only for 10–11% respondents.

The main strength of our questionnaire study lies in the large number of responses gathered from physicians who specialize in endocrinology or gynaecology across multiple countries including members of highly respected societies. However, it is important to acknowledge the study's limitations. The distribution of questionnaire responses across different countries was uneven, with over 10 respondents in seven countries (six European countries and the USA), 5–9 from seven countries, and 1–3 in the remaining 31 countries. This anomaly may be partially attributable to 11 of the latter countries being of LMI or UMI status, with fewer paediatric endocrinologists.

Another point is that the study was conducted during the immediate post-COVID-19 era, which was characterized by numerous supply challenges. However, it is noteworthy that this particular problem was not cited as a problem among respondents who had the option to report issues in the "Other" answer category. It appears therefore that availability, rather than supply, was the principal problem. Certain questions did not include all available preparation options. For instance, when examining responses to questions regarding the preferred route of oestrogen administration, we found that they did not account for various transdermal estradiol options (e.g., patches, gel, spray) and when respondents chose the "Other" option, we observed that some individuals felt the need to specify their choices. Another problem was the availability of preparations. Some respondents elaborated on their answers, explaining that they could only indicate preparations they are currently using and were unsure about the accessibility of other preparations in their respective countries. Furthermore, the description of the responses is limited by the inability to discern the rationale behind the preference for a specific type of oestrogen, progestogen, or route of administration. We have demonstrated that the lack of availability of preparations may be one of the factors influencing the decision on route and dose of oestrogen therapy. However, patient preference and cost considerations can also contribute to this decision. In summary, we believe that

this work underlines the current lack of, and need for, appropriate oestrogen and progestogen preparations necessary for the care of girls with hypogonadism.

Acknowledgments

We thank all healthcare specialists who participated in the survey.

Statement of Ethics

This study protocol was reviewed, and the need for approval was waived by the bioethics committee of the Medical University of Silesia (No. BNW/NWN/0052/KB/13/24). The need for informed consent was waived by the bioethics committee of the Medical University of Silesia (BNW/NWN/0052/KB/13/24).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

A.M.G.-S., D.M., B.Ö.K., J.A.E.M.V., T.C.J.S., M.Wa., S.V., C.B., A.S., and M.D.C.D. designed and distributed the survey, interpreted the results, and reviewed and edited the manuscript. A.M.G.-S. and M.Wi. analysed the data, prepared the draft of the manuscript, and created tables and figures.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of respondents, but are available from the authors (AGS, agawlik@mp.pl; MWi, mallgorzatawegiel@gmail.com), upon reasonable request.

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