Prevalence and treatment of central hypogonadism and hypoandrogenism in women with hypopituitarism

Catharina Olivius[1], Kerstin Landin-Wilhelmsen[2], Daniel S. Olsson[2], Gudmundur Johannsson[2], Åsa Tivesten[2].

[1] Department of Medicine, Hospital of Halland, Kungsbacka, Sweden. [2] Department of Endocrinology, Sahlgrenska University Hospital and Department of Internal Medicine and Clinical Nutrition, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden.

Correspondence: Catharina Olivius, Department of Medicine, Hospital of Halland/Kungsbacka, Tölövägen 3, S-434 80 Kungsbacka, Sweden. Tel: +46 300 565000. E-mail: catharina.olivius@regionhalland.se

ORCIDs of the authors: Catharina Olivius 0000-0003-3324-8793, Kerstin Landin-Wilhelmsen 0000-0003-1998-5105, Daniel S. Olsson 0000-0002-9734-0786, Gudmundur Johannsson 0000-0003-3484-8440, Åsa Tivesten 0000-0002-8318-0486.

Acknowledgements: This study was supported by the Swedish Research Council, the Swedish Heart-Lung Foundation, the ALF (Avtal om Läkarutbildning och Forskning) research grant, Gothenburg, the Marianne and Marcus Wallenberg Foundation, AFA Insurance, the Novo Nordisk Foundation, the Inga-Britt and Arne Lundberg Foundation and the Scientific Council in the Region of Halland.

Conflict of interest statement: The authors declare that they have no conflict of interest.

Abstract

Purpose: Women with hypopituitarism have increased morbidity and mortality, and hypogonadism has been suggested to be a contributing mechanism. The purpose of this study was to investigate the prevalence of central hypogonadism and hypoandrogenism in women with hypopituitarism at a single Swedish center.

Methods: All consecutive women (n = 184) who commenced **growth hormone (GH)** replacement therapy at Sahlgrenska University Hospital in Gothenburg between 1995 and 2015 were included. In accordance with the Endocrine Society Clinical Practice Guidelines, strict criteria, based on menstrual history combined with laboratory measurements, were used to define central hypogonadism. Hypoandrogenism was defined as subnormal levels of dehydroepiandrosterone sulfate and/or androstenedione.

Results: Central hypogonadism was present in 78% of the women, in 75% of those ≤ 52 years and in 82% of those > 52 years of age. Hypoandrogenism was found in 61% of all the women and in 92% of those with **adrenocorticotropic hormone (ACTH)** deficiency. The estrogen substitution rate in hypogonadal women ≤ 52 years was lower than the hormonal substitution rate in the other pituitary hormone axes (74% versus 100%, $P < 0.001$). The use of estrogen substitution tended to decrease between 2000 and 2016. Few women received androgen treatment.

Conclusions: In this first study of hypogonadism in women with hypopituitarism, using stringent diagnostic criteria for hypogonadism, the prevalence of central hypogonadism and low androgen levels was high and estrogen substitution was insufficient. Further studies are needed to elucidate the importance of hypogonadism and insufficient sex steroid replacement for the increased morbidity in hypopituitary women.

Keywords: Hypopituitarism, women, hypogonadism, estrogens, androgens, estrogen replacement therapy.

1. Introduction

Hypopituitarism has been associated with increased mortality, mainly due to the increased risk of death from cardiovascular events and infections [1-4]. Likely due to optimized treatment regimens, mortality in men with hypopituitarism has decreased in recent decades and now approaches the mortality of the background population [5-7]. In contrast, women with hypopituitarism still have increased mortality, mainly due to the increased risk of cardiovascular events [3,5-8]. In addition, women with hypopituitarism have poorer bone mineral density with a doubled fracture risk, compared with no increased fracture risk in hypopituitary men [9,10], and in a study from our own center, women with hypopituitarism with untreated hypogonadism had significantly more fractures, in contrast to women with an intact gonadal axis or estrogen treatment [11]. A nationwide Swedish study recently showed that women with hypopituitarism have a relatively higher risk of diabetes mellitus type 2, myocardial infarction, cerebral infarction and fractures, compared with hypopituitary men [10].

The reason why hypopituitary women have higher morbidity and mortality is not fully understood. Several theories have been discussed [5,12,13]: Firstly, estrogen deficiency may have been underdiagnosed and/or undersubstituted; secondly, low androgen levels in women with hypopituitarism may need substitution; and, thirdly, other pituitary deficiencies, such as hypocortisolism and **growth hormone (GH)** deficiency, may have been underdiagnosed and/or suboptimally treated in women [13,14].

Sex hormone substitution therapy to female patients is the main difference between the treatment of men and women, and some studies support the theory that hypogonadism is a key factor behind the increased mortality in hypopituitary women [3,15]. Surprisingly few studies have provided a comprehensive description of the prevalence and treatment of hypogonadism in women with hypopituitarism [14,8], and no earlier studies have applied the stringent criteria for central hypogonadism in the Endocrine Society's Clinical Practice Guidelines [16]. In addition, to our knowledge, there are no other studies presenting prevalence numbers on hypoandrogenism in women with hypopituitarism.

The aim of this study was to estimate the prevalence of central hypogonadism and hypoandrogenism in a cohort of Swedish women with hypopituitarism, and the extent to which the women received estrogen and androgen substitution.

2. Materials and methods

Patient cohort

At the Centre for Endocrinology and Metabolism (CEM), Sahlgrenska University Hospital, a registry of all **adult** patients who received treatment with GH started in 1990 (The Gothenburg Pituitary study). All female patients (n = 281) who started GH treatment at the CEM after 1995 were evaluated for the present study. Patients who started their treatment before 1995 were not included due to incomplete documentation during the first years of the registry. The exclusion criteria were hormonally active pituitary adenoma, except prolactinoma (n = 38), extrapituitary tumors or malignancies, except dermoid cysts and craniopharyngioma (n = 44), serious systemic diseases (n = 7), and malformations (n = 7). One patient died before any data had been registered. After exclusion of these patients, 184 women **(age range 17-77 years)** were included in the study. The date when GH therapy was initiated was denoted the "baseline" of the study. The local recommendation has been to initiate estrogen replacement at least three months before GH therapy. The patients were examined (including anthropometry) by a physician and fasting serum was collected for laboratory analyses at baseline and after six months, one year, and 2, 3, 5, 7, 10, 12, 17, 20 and 25 years of follow-up.

Data collection

An endocrinology specialist (Dr. Olivius) made a retrospective evaluation of data in the medical records and in the registry. Hormone deficiencies and how they were diagnosed, hormone substitution treatment, hormonal levels and cigarette use were registered. Premenopausal age was defined as being 52 years or younger and postmenopausal age as being older than 52 years [17].

Diagnosis of central hypogonadism.

The retrospective evaluation of central hypogonadism was performed using the following stringent criteria, based on the recommendations in the Endocrine Society's Clinical Practice Guidelines [16]: 1) In premenopausal women (≤ 52 years of age), amenorrhea or severe oligomenorrhea without other gynecological explanation, supported by available measurements of serum estradiol, **luteinizing hormone (LH), follicle-stimulating hormone (FSH),** and, in a few cases, gonadotropin-releasing hormone stimulation test (n = 4); 2) in postmenopausal women (> 52 years), amenorrhea with absence of both high FSH and LH, and no estrogen treatment; 3) in childhood-onset hypopituitarism, absent puberty and puberty induction; and 4)

panhypopituitarism, where other assessment was impossible, e.g., due to absence of FSH/LH measurements in postmenopausal women or estrogen treatment at the time of evaluation. Deficiencies of **adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH),** GH and **antidiuretic hormone (ADH)** were assessed by the attending physician.

Lifetime assessment of estrogen substitution therapy

For the women fulfilling the criteria of central hypogonadism at any time point, a life-time assessment of the number of years with central hypogonadism was performed, using an integrated assessment as described above. Similarly, a life-time assessment of the number of years with estrogen substitution therapy was performed. The implementation of estrogen substitution was calculated as the total number of **"estrogen-substituted years"** divided by the total number of **"estrogen-deficient years"** until 52 years of age **In essence, this is an estimate how well guidelines have been followed.**

Laboratory analyses and definition of low androgen levels

At baseline; i.e., the start of GH treatment, the routine laboratory analyses included serum testosterone, dehydroepiandrosterone sulfate (DHEAS) and androstenedione. The reference ranges for all three androgens varied between laboratories and changed several times during follow-up, making direct comparisons of androgen levels impossible. The DHEAS/androstenedione levels in the study were thus presented as being below, within or above the current reference ranges. The reference ranges of the DHEAS analyses were age-specific throughout the study period. For androstenedione, the reference ranges were age-specific until 2009. The testosterone analyses used at the time of this study had reference ranges with no exact lower reference limit, which made discrimination between low and normal testosterone levels difficult. Instead, testosterone levels were defined as being measurable or unmeasurable, according to the current lower limit of quantification (< 0.35, < 0.4, < 0.7, or < 1.0 nmol/L). Serum estradiol, LH and FSH were not routinely analyzed at baseline, but had often been measured earlier in the patient's medical history.

Having a low androgen level was defined in the present study as having a DHEAS and/or androstenedione level below the lower reference range, or ongoing androgen treatment at the time of androgen measurement, assuming these women had low androgen levels originally. Testosterone levels were not included in this definition, for the reasons detailed above.

Ethics

This study was approved by the Regional Ethical Review Board in Gothenburg, Sweden.

Statistical analysis

To determine the relationship between categorical variables, the Chi-square test and Fisher's exact test were used. A p value of < 0.05 was considered statistically significant. Statistical analyses were performed using the IBM SPSS (version 24; SPSS Institute) software.

3. Results

Baseline characteristics

The mean (± SD) age at baseline was 47.5 ± 15.6 years, with an age distribution as illustrated in Figure 1. In the premenopausal age group (≤ 52 years; n=108) the mean age was 37.0 ± 10.7 years and in the postmenopausal age group (> 52 years; n= 76) the mean age was 62.6 ± 6.2 years. Due to the inclusion criteria of the registry, all patients had GH deficiency, 70% had TSH deficiency, 52% ACTH deficiency, 24% ADH deficiency, and 46% had panhypopituitarism (Table 1). Sixteen patients died during follow-up, eight patients moved and three were lost to follow-up for other reasons.

Prevalence of central hypogonadism

Using our criteria (see Methods), 143 women (78% of the participants) were determined to have central hypogonadism. The diagnosis of central hypogonadism was mainly based on menstrual history in 60 (42%) of the patients, low FSH and LH despite postmenopausal amenorrhea in 62 (43%), childhood-onset hypopituitarism with puberty induction in 18 (13%), and panhypopituitarism, when other assessment was impossible, in three patients (2%).

In the premenopausal age group (≤ 52 years), 81/108 (75%) were hypogonadal; 76 were defined as hypogonadal at baseline and five patients developed central hypogonadism later than baseline. In the postmenopausal age group (> 52 years), 62/76 (82%) were hypogonadal (premenopausal women vs. postmenopausal women; $P = 0.29$). In the older age group (> 52 years), 88% had low LH and 83% had low FSH according to the postmenopausal reference range of the local laboratory.

Estrogen treatment at baseline

At the baseline visit; i.e., at the start of GH treatment when estrogen treatment should have been initiated according to local guidelines, 56/76 (74%) of the hypogonadal women of premenopausal age (≤ 52 years) were treated with estrogen. Treatment was more common among relatively younger women; 43/51 (84%) of the women < 45 years versus 13/25 (52%) of the women aged 45-52 years ($P < 0.01$). The substitution treatment rate was significantly lower in the gonadotropic axis compared with the other pituitary axes, 74% versus 100% ($P < 0.001$, Table 1). The reasons for not treating the remaining 20 patients with estrogen were unclear medical

records for eight patients, adverse side effects for four, near menopausal age for three, partial deficiency with sporadic menstruations for three, earlier cerebral infarction for one and fear of side effects for one patient(s).

Among the older women with central hypogonadism (>52 years), 15/62 (24%) had estrogen treatment at the time of the baseline visit.

Estrogen treatment over time

To analyze estrogen treatment over time, the proportion of all women who received estrogen treatment in the year 1996, 2000, 2004, 2008, 2012 and 2016 was recorded (Figure 2). In the older age group (all women > 52 years of age), the estrogen treatment rate decreased sharply during the same time period ($P < 0.001$, Figure 2). There was a trend towards less estrogen substitution treatment also in the younger women (≤ 52 years) with central hypogonadism, from 91% in the year 2000 to 73% in 2016 ($P = 0.12$).

Lifetime assessment of estrogen substitution therapy

For 91 women in the study, estrogen therapy was indicated at any time before or after the study had started due to central hypogonadism and age ≤ 52 years at the time of this diagnosis. The implementation of estrogen substitution, calculated as the total number of **"estrogen-substituted years"** divided by the total number of **"estrogen-deficient years"** until 52 years of age, was 809/1253 (65%). It is noteworthy that **only** 54% of the women with an indication for estrogen treatment received estrogen 75-100% of the time, while 46% received estrogen treatment 0-74% of the time with a treatment indication.

Estrogen substitution therapy was prescribed and followed up in collaboration with a gynecologist. At baseline, the treatment was administered as oral estrogen in 55/78 (71%) patients, transdermal estrogen in the form of patches or gel in 14/78 (18%) patients, and as combined oral contraceptives in 9/78 (12%) patients. The active substance was estradiol in 61 (78%) of the medications, ethinylestradiol in nine (12%), which were the oral contraceptives, conjugated estrogens in four (5%), estriol in three (4%) and tibolone in one patient (1%).

Prevalence of low androgen levels

A majority of the patients in whom androgens had been measured had levels below the lower reference limit of DHEAS (53%), androstenedione (51%) or unmeasurable levels of testosterone (62%), **and the prevalence of**

low levels was similar in the younger (≤ 52 years) and older (>52 years) age groups. Five women had ongoing androgen treatment at the time of measurement.

Low androgen levels, defined as low DHEAS and/or low androstenedione and/or ongoing androgen treatment, were found in 99/163 (61%) of the women with DHEAS and/or androstenedione measurements **available (Table 2)**. For sixteen patients (9%), no androgen levels were recorded.

Of the women with ongoing estrogen treatment, 49/64 (77%) had low DHEAS and/or androstenedione levels, compared with 45/96 (47%) of those with no estrogen treatment at the time of measurement. Low androgen levels were more common among patients with ACTH and/or LH/FSH deficiency (central hypogonadism; **Table 2**).

Androgen treatment

Of all the women, 32/184 (17%) received androgen treatment at any time during follow-up; 26 were treated with dehydroepiandrosterone (DHEA), three with testosterone and three with other androgenic steroids. Of the 32 women who received androgen treatment, 18 patients experienced positive effects and continued treatment and 14 discontinued treatment due to a lack of effect (n = 4), unwanted side effects such as acne, nausea and hair loss (n = 3), or for unknown reasons (n = 7).

To analyze androgen treatment over time, the proportion of all women who received androgen treatment in the year 1996, 2000, 2004, 2008, 2012 and 2016 was recorded, showing no change in the substitution rate over time (Figure 2).

4. Discussion

In this large and well-defined patient cohort of women with GH deficiency due to hypopituitarism, a majority had central hypogonadism, according to the criteria of the Endocrine Society's Clinical Practice Guidelines [16]. Low androgen levels were common in the study cohort. The substitution treatment rate was significantly lower in the LH/FSH axis than in the other pituitary axes. The proportion of younger women (≤ 52 years) with central hypogonadism who received estrogen therapy tended to decrease from 2000 to 2016. Few of the women received androgen treatment.

To our knowledge, this is this first study using stringent criteria to define central hypogonadism, based on the Endocrine Society's Clinical Practice Guidelines [16], in a cohort of women with hypopituitarism. Despite that, the prevalence of hypogonadism in the present study, 78%, is higher than previously reported in other studies. A Danish study reported that 38% of the women (0-91 years, n = 1794) with GH deficiency had hypogonadism [8], and in another study of women (18-50 years, n = 628) with GH deficiency, 50% had hypogonadism [14]. A reason for this discrepancy between the present and previous studies may be that partial gonadal deficiencies are easily missed, e.g., due to the cyclic variations in estradiol, LH and FSH, and the fact that partially deficient women may still have oligomenorrhea [16]. Indeed, the diagnostic criteria for hypogonadism differed between these three studies [8,14]. The validity of our data is strengthened by the fact that we found a similar prevalence of hypogonadism in younger (75%) and older (82%) women. While both low LH and FSH levels were required for a diagnosis of central hypogonadism in our study, the high prevalence figure in the older age group is further supported by the fact that as many as 88% of the women > 52 years had LH levels below the normal postmenopausal range.

According to the clinical guidelines, estrogen replacement is recommended in hypopituitary women with hypogonadism until the age of the natural menopause [16]. The substitution treatment rate among women of premenopausal age in the present study was significantly lower in the gonadal axis (74%) than in the other pituitary axes. This figure is similar to that of a Danish study of GH-deficient patients from 2007, where the proportion of women with central hypogonadism < 55 years of age who received estrogen substitution was 78% [8]. In a study of hypopituitary patients of all ages, studied retrospectively between 1967 and 1994, only 27% of the women with hypogonadism received estrogen substitution treatment, possibly illustrating a historically even lower substitution treatment rate [18]. In a lifetime assessment of estrogen substitution, we found that only half of the women received estrogen treatment during 75-100% of their estrogen-deficient years,

further illustrating that most women in our study did not receive adequate estrogen substitution therapy; to our knowledge, no similar analyses have previously been performed.

Several studies suggest cardiovascular benefits of estrogen replacement therapy in younger [19,20], but not older, women with central hypogonadism. Estrogen replacement therapy in hypogonadal women also protects against fractures [11,21,22]. It may thus be speculated that the undertreatment with estrogen could be one of the factors behind the increased morbidity and mortality among women with hypopituitarism.

One reason for the undertreatment with estrogen in relation to the guidelines could be that estrogen therapy is prescribed by a gynecologist and not by the endocrinologist, potentially leading to poorer control of the substitution treatment. A second reason could be adverse side effects, which was the most commonly reported reason for not using estrogen therapy in this study. A third reason could be the fear of causing a late-term increased risk of breast cancer, thromboembolism or cardiovascular events, especially after the Women's Health Initiative (WHI) study was published in 2002 [23]. Indeed, in the present study, the decreased estrogen therapy to women > 52 years with hypogonadism might reflect a reluctance towards estrogen treatment after publication of the WHI results. Estrogen supplementation use in postmenopausal women of the general population in the same region decreased from 37% to 10% during approximately the same time period (1995 to 2008) [24]. In parallel, the fracture frequency increased from 17% to 29% [24]. Other studies have shown a similar, decreasing trend in estrogen use in postmenopausal and hysterectomized women from 2002 onwards [25]. One study found that the discontinuance rate of estrogen replacement therapy was lower in the "late post-WHI era", 2010-2013, compared with the "early post-WHI era", 2007-2009, which might indicate a change towards a somewhat more positive attitude towards estrogen treatment in the most recent years [26]; however, no similar trend was seen in our cohort.

A majority of the women in this study had low DHEAS and/or androstenedione levels. There are few studies reporting prevalence rates of low androgen levels in hypopituitary women. One study found unmeasurable testosterone levels in 55% of the women with hypopituitarism [12]. In the present study, 70% of the women had unmeasurable testosterone levels. Importantly, unmeasurable testosterone levels, may—depending on the analysis method used—be a normal finding in women [27]. Recently, highly sensitive assays have been developed for analyses of low testosterone levels [28], and an important task for future studies will be to assess testosterone levels in women with hypopituitarism.

Low androgen levels may reflect deficiency of LH/FSH and/or ACTH and thereby insufficient androgen production by the ovaries and adrenals. Low DHEAS and/or androstenedione levels were consequently

more common in women with deficiency of LH/FSH, ACTH, or both. Low DHEAS/androstenedione levels were also more prevalent in the women with ongoing estrogen treatment than in the women without, and even more so in women with both central hypogonadism and ongoing estrogen treatment. The reason for this could be that estrogen treatment suppresses the androgen levels [29], and/or that central hypogonadism also manifests itself as androgen deficiency. Treatment with corticosteroids also suppresses androgen levels in women, which, in addition to the absence of ACTH, may contribute to lower androgen levels in ACTH-deficient women [27].

Few women received androgen treatment, and the androgen use did not change over time. There is currently no established laboratory definition of androgen deficiency in women. Hence, there is no consensus on whether women with hypopituitarism and low androgen levels should be prescribed androgen substitution or not. Limited data support a clinical improvement from androgen supplementation, but no studies of long-term benefits and risks are available [16,27]. However, androgens are important for bone mass in women and low androgen levels may be a contributing factor to the increased fracture risk in hypopituitary women [30]. Indeed, testosterone levels have been shown to correlate positively with bone mineral density, especially in older postmenopausal women [31]. Androgen receptor deficiency leads to increased atherosclerosis, dyslipidemia and adiposity in female mice, suggesting that androgens may play an important cardiometabolic role in women [32]. In a randomized controlled study of transdermal testosterone in women with hypopituitarism, testosterone increased bone mass, sexual function and quality of life, and decreased fasting insulin and insulin resistance [12,33]. In a placebo-controlled study from our own center, a low dose of DHEA to hypopituitary women resulted in improved alertness, stamina, initiative and sexual relations in women with hypopituitarism, as reported by their spouses [34]. It remains unclear whether androgen deficiency has an impact on morbidity and mortality in hypopituitary women. Improved analysis methods for androgens may contribute to the delineation of a possible androgen deficiency syndrome in women. This might facilitate future studies of the long-term benefits and risks of androgen supplementation.

A limitation of the present study is that only GH-**treated** women were included and not all women with hypopituitarism at our center**. Unfortunately, no similar data were available for those without GH treatment.** This may have left out some of the older patients and those with poor general health, as well as patients with less severe pituitary disease. Those selected for GH replacement are generally younger and have more severe hypopituitarism [35]. A weakness in the comparison of treatment rates is that central hypogonadism was assessed retrospectively, while other pituitary deficiencies were determined by the attending physician**. Another limitation of the study was that laboratory methods and reference ranges changed during the**

study, making direct comparisons of hormone levels impossible. The strengths of the study include the consecutive inclusion of 184 well-controlled patients, followed up at one single center, and the long-term follow-up.

In conclusion, central hypogonadism and low androgen levels were common in this unique study of women with hypopituitarism. The substitution treatment rate was lower in the LH/FSH axis than in the other pituitary axes. The proportion of women receiving estrogen therapy decreased between the years 2000 to 2016 in older women. Few women received androgen therapy. As women with hypopituitarism have a worse overall prognosis than men, further studies are needed to elucidate the importance of hypogonadism and sex steroid replacement for outcomes in women with hypopituitarism.

7. References

1. Rosen, T., Bengtsson, B.A.: Premature mortality due to cardiovascular disease in hypopituitarism. Lancet **336**(8710), 285-288 (1990).
2. Bulow, B., Hagmar, L., Mikoczy, Z., Nordstrom, C.H., Erfurth, E.M.: Increased cerebrovascular mortality in patients with hypopituitarism. Clin Endocrinol (Oxf) **46**(1), 75-81 (1997).
3. Tomlinson, J.W., Holden, N., Hills, R.K., Wheatley, K., Clayton, R.N., Bates, A.S., Sheppard, M.C., Stewart, P.M.: Association between premature mortality and hypopituitarism. West Midlands Prospective Hypopituitary Study Group. Lancet **357**(9254), 425-431 (2001).
4. Burman, P., Mattsson, A.F., Johannsson, G., Hoybye, C., Holmer, H., Dahlqvist, P., Berinder, K., Engstrom, B.E., Ekman, B., Erfurth, E.M., Svensson, J., Wahlberg, J., Karlsson, F.A.: Deaths among adult patients with hypopituitarism: hypocortisolism during acute stress, and de novo malignant brain tumors contribute to an increased mortality. J Clin Endocrinol Metab **98**(4), 1466-1475 (2013). doi:10.1210/jc.2012-4059
5. Nielsen, E.H., Lindholm, J., Laurberg, P.: Excess mortality in women with pituitary disease: a meta-analysis. Clin Endocrinol (Oxf) **67**(5), 693-697 (2007). doi:10.1111/j.1365-2265.2007.02947.x
6. Olsson, D.S., Nilsson, A.G., Bryngelsson, I.L., Trimpou, P., Johannsson, G., Andersson, E.: Excess Mortality in Women and Young Adults With Nonfunctioning Pituitary Adenoma: A Swedish Nationwide Study. J Clin Endocrinol Metab **100**(7), 2651-2658 (2015). doi:10.1210/jc.2015-1475
7. Olsson, D.S., Andersson, E., Bryngelsson, I.L., Nilsson, A.G., Johannsson, G.: Excess mortality and morbidity in patients with craniopharyngioma, especially in patients with childhood onset: a population-based study in Sweden. J Clin Endocrinol Metab **100**(2), 467-474 (2015). doi:10.1210/jc.2014-3525
8. Stochholm, K., Gravholt, C.H., Laursen, T., Laurberg, P., Andersen, M., Kristensen, L.O., Feldt-Rasmussen, U., Christiansen, J.S., Frydenberg, M., Green, A.: Mortality and GH deficiency: a nationwide study. Eur J Endocrinol **157**(1), 9-18 (2007). doi:10.1530/EJE-07-0013
9. Holmer, H., Svensson, J., Rylander, L., Johannsson, G., Rosen, T., Bengtsson, B.A., Thoren, M., Hoybye, C., Degerblad, M., Bramnert, M., Hagg, E., Engstrom, B.E., Ekman, B., Thorngren, K.G., Hagmar, L., Erfurth, E.M.: Fracture incidence in GH-deficient patients on complete hormone replacement including GH. J Bone Miner Res **22**(12), 1842-1850 (2007). doi:10.1359/jbmr.070811
10. Olsson, D.S., Bryngelsson, I.L., Ragnarsson, O.: Higher incidence of morbidity in women than men with non-functioning pituitary adenoma: a Swedish nationwide study. Eur J Endocrinol **175**(1), 55-61 (2016). doi:10.1530/EJE-16-0173
11. Rosen, T., Wilhelmsen, L., Landin-Wilhelmsen, K., Lappas, G., Bengtsson, B.A.: Increased fracture frequency in adult patients with hypopituitarism and GH deficiency. Eur J Endocrinol **137**(3), 240-245 (1997).
12. Miller, K.K., Biller, B.M., Beauregard, C., Lipman, J.G., Jones, J., Schoenfeld, D., Sherman, J.C., Swearingen, B., Loeffler, J., Klibanski, A.: Effects of testosterone replacement in androgen-deficient women with hypopituitarism: a randomized, double-blind, placebo-controlled study. J Clin Endocrinol Metab **91**(5), 1683-1690 (2006). doi:10.1210/jc.2005-2596
13. Ragnarsson, O., Nystrom, H.F., Johannsson, G.: Glucocorticoid replacement therapy is independently associated with reduced bone mineral density in women with hypopituitarism. Clin Endocrinol (Oxf) **76**(2), 246-252 (2012). doi:10.1111/j.1365-2265.2011.04174.x
14. Mah, P.M., Webster, J., Jonsson, P., Feldt-Rasmussen, U., Koltowska-Haggstrom, M., Ross, R.J.: Estrogen replacement in women of fertile years with hypopituitarism. J Clin Endocrinol Metab **90**(11), 5964-5969 (2005). doi:10.1210/jc.2005-1207

15. Jasim, S., Alahdab, F., Ahmed, A.T., Tamhane, S., Prokop, L.J., Nippoldt, T.B., Murad, M.H.: Mortality in adults with hypopituitarism: a systematic review and meta-analysis. Endocrine **56**(1), 33-42 (2017). doi:10.1007/s12020-016-1159-3
16. Fleseriu, M., Hashim, I.A., Karavitaki, N., Melmed, S., Murad, M.H., Salvatori, R., Samuels, M.H.: Hormonal Replacement in Hypopituitarism in Adults: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab **101**(11), 3888-3921 (2016). doi:10.1210/jc.2016-2118
17. Palacios, S., Henderson, V.W., Siseles, N., Tan, D., Villaseca, P.: Age of menopause and impact of climacteric symptoms by geographical region. Climacteric **13**(5), 419-428 (2010). doi:10.3109/13697137.2010.507886
18. Bates, A.S., Van't Hoff, W., Jones, P.J., Clayton, R.N.: The effect of hypopituitarism on life expectancy. J Clin Endocrinol Metab **81**(3), 1169-1172 (1996). doi:10.1210/jcem.81.3.8772595
19. Boardman, H.M., Hartley, L., Eisinga, A., Main, C., Roque i Figuls, M., Bonfill Cosp, X., Gabriel Sanchez, R., Knight, B.: Hormone therapy for preventing cardiovascular disease in post-menopausal women. Cochrane Database Syst Rev(3), CD002229 (2015). doi:10.1002/14651858.CD002229.pub4
20. Rivera, C.M., Grossardt, B.R., Rhodes, D.J., Brown, R.D., Jr., Roger, V.L., Melton, L.J., 3rd, Rocca, W.A.: Increased cardiovascular mortality after early bilateral oophorectomy. Menopause **16**(1), 15-23 (2009). doi:10.1097/gme.0b013e31818888f7
21. Lindsay, R., Hart, D.M., Forrest, C., Baird, C.: Prevention of spinal osteoporosis in oophorectomised women. Lancet **2**(8205), 1151-1154 (1980).
22. Tuppurainen, M., Kroger, H., Honkanen, R., Puntila, E., Huopio, J., Saarikoski, S., Alhava, E.: Risks of perimenopausal fractures--a prospective population-based study. Acta Obstet Gynecol Scand **74**(8), 624-628 (1995).
23. Rossouw, J.E., Anderson, G.L., Prentice, R.L., LaCroix, A.Z., Kooperberg, C., Stefanick, M.L., Jackson, R.D., Beresford, S.A., Howard, B.V., Johnson, K.C., Kotchen, J.M., Ockene, J., Writing Group for the Women's Health Initiative, I.: Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA **288**(3), 321-333 (2002).
24. Trimpou, P., Lindahl, A., Lindstedt, G., Olerod, G., Wilhelmsen, L., Landin-Wilhelmsen, K.: Secular trends in sex hormones and fractures in men and women. Eur J Endocrinol **166**(5), 887-895 (2012). doi:10.1530/EJE-11-0808
25. Kyvernitakis, I., Kostev, K., Hars, O., Albert, U.S., Hadji, P.: Discontinuation rates of menopausal hormone therapy among postmenopausal women in the post-WHI study era. Climacteric **18**(5), 737-742 (2015). doi:10.3109/13697137.2015.1037267
26. Kyvernitakis, I., Kostev, K., Hars, O., Albert, U.S., Kalder, M., Hadji, P.: Persistency with estrogen replacement therapy among hysterectomized women after the Women's Health Initiative study. Climacteric **18**(6), 826-834 (2015). doi:10.3109/13697137.2015.1081164
27. Wierman, M.E., Arlt, W., Basson, R., Davis, S.R., Miller, K.K., Murad, M.H., Rosner, W., Santoro, N.: Androgen therapy in women: a reappraisal: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab **99**(10), 3489-3510 (2014). doi:10.1210/jc.2014-2260
28. Nilsson, M.E., Vandenput, L., Tivesten, A., Norlen, A.K., Lagerquist, M.K., Windahl, S.H., Borjesson, A.E., Farman, H.H., Poutanen, M., Benrick, A., Maliqueo, M., Stener-Victorin, E., Ryberg, H., Ohlsson, C.: Measurement of a Comprehensive Sex Steroid Profile in Rodent Serum by High-Sensitive Gas Chromatography-Tandem Mass Spectrometry. Endocrinology **156**(7), 2492-2502 (2015). doi:10.1210/en.2014-1890
29. Zimmerman, Y., Eijkemans, M.J., Coelingh Bennink, H.J., Blankenstein, M.A., Fauser, B.C.: The effect of combined oral contraception on testosterone levels in healthy women: a systematic review and meta-analysis. Hum Reprod Update **20**(1), 76-105 (2014). doi:10.1093/humupd/dmt038

30. Miller, K.K., Biller, B.M., Hier, J., Arena, E., Klibanski, A.: Androgens and bone density in women with hypopituitarism. J Clin Endocrinol Metab **87**(6), 2770-2776 (2002). doi:10.1210/jcem.87.6.8557
31. Khosla, S., Riggs, B.L., Robb, R.A., Camp, J.J., Achenbach, S.J., Oberg, A.L., Rouleau, P.A., Melton, L.J., 3rd: Relationship of volumetric bone density and structural parameters at different skeletal sites to sex steroid levels in women. J Clin Endocrinol Metab **90**(9), 5096-5103 (2005). doi:10.1210/jc.2005-0396
32. Fagman, J.B., Wilhelmson, A.S., Motta, B.M., Pirazzi, C., Alexanderson, C., De Gendt, K., Verhoeven, G., Holmang, A., Anesten, F., Jansson, J.O., Levin, M., Boren, J., Ohlsson, C., Krettek, A., Romeo, S., Tivesten, A.: The androgen receptor confers protection against diet-induced atherosclerosis, obesity, and dyslipidemia in female mice. FASEB J **29**(4), 1540-1550 (2015). doi:10.1096/fj.14-259234
33. Miller, K.K., Biller, B.M., Schaub, A., Pulaski-Liebert, K., Bradwin, G., Rifai, N., Klibanski, A.: Effects of testosterone therapy on cardiovascular risk markers in androgen-deficient women with hypopituitarism. J Clin Endocrinol Metab **92**(7), 2474-2479 (2007). doi:10.1210/jc.2007-0195
34. Johannsson, G., Burman, P., Wiren, L., Engstrom, B.E., Nilsson, A.G., Ottosson, M., Jonsson, B., Bengtsson, B.A., Karlsson, F.A.: Low dose dehydroepiandrosterone affects behavior in hypopituitary androgen-deficient women: a placebo-controlled trial. J Clin Endocrinol Metab **87**(5), 2046-2052 (2002). doi:10.1210/jcem.87.5.8494
35. Olsson, D.S., Trimpou, P., Hallen, T., Bryngelsson, I.L., Andersson, E., Skoglund, T., Bengtsson, B.A., Johannsson, G., Nilsson, A.G.: Life expectancy in patients with pituitary adenoma receiving growth hormone replacement. Eur J Endocrinol **176**(1), 67-75 (2017). doi:10.1530/eje-16-0450

8. Tables

Table 1 Characteristics of the cohort of women with hypopituitarism

	All women, baseline (n = 184)
Age, mean (range)	47.5 (17-77)
Body mass index, kg/cm^2 mean (range)	29.4 (18.0-49.1)
Current smoking, n (%)	34 (18)
Diagnosis, n (%):	
Non-functioning pituitary adenoma	63 (34)
Idiopathic growth hormone deficiency	25 (14)
Craniopharyngeoma	23 (13)
Prolactinoma	17 (9)
Empty sella	16 (9)
Pituitary cyst	14 (8)
Hypophysitis	12 (7)
Sheehan's syndrome	10 (5)
Other[a]	4 (2)
ACTH	
Deficiency (number, % of all)	96 (52)
Substitution (number, % of the deficient)	96 (100)
TSH	
Deficiency (number, % of all)	129 (70)
Substitution (number, % of the deficient)	129 (100)
GH	
Deficiency (number, % of all)	184 (100)
Substitution (number, % of the deficient)	184 (100)
ADH	
Deficiency (number, % of all)	44 (24)
Substitution (number, % of the deficient)	44 (100)
LH/FSH	
Deficiency (central hypogonadism, number, % of all)[b]	143 (78)
Substitution (number, % of the deficient women ≤ 52 years, n = 76)	56 (74)
Panhypopituitarism[c] (number, % of all)	85 (46)

[a] Kallman's syndrome (n = 1), dermoid cyst (n = 1), traumatic brain injury (n = 2).

[b] Central hypogonadism. According to the retrospective evaluation.

[c] Deficiency of ACTH, TSH, GH and LH/FSH.

Table 2 Prevalence of low androgen levels[a] in all women with hypopituitarism, women with ACTH deficiency, LH/FSH deficiency (central hypogonadism), or both

	Low androgen levels[a], n (%)
Women	
All	99/163 (61)
With ACTH deficiency	82/89 (92)
With LH/FSH deficiency	
All	92/126 (73)
With estrogen treatment[b]	50/59 (85)
With ACTH and LH/FSH deficiency	77/83 (93)
With panhypopituitarism	73/78 (94)

Only women with available measurements of DHEAS and/or androstenedione were included in this analysis.

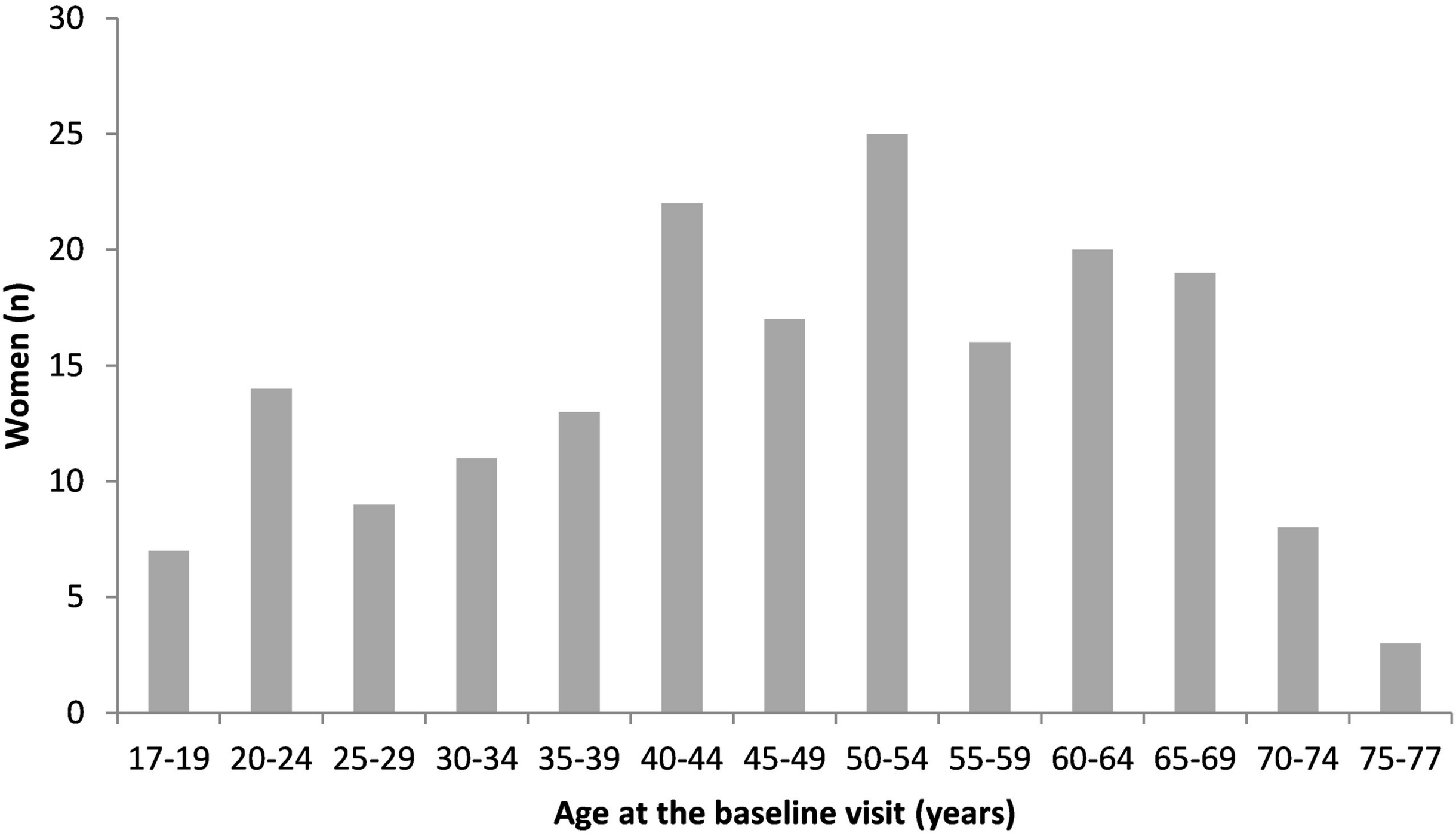
[a] Low (below lower reference limit) level of DHEAS and/or androstenedione, or ongoing androgen treatment (n = 5) at baseline.

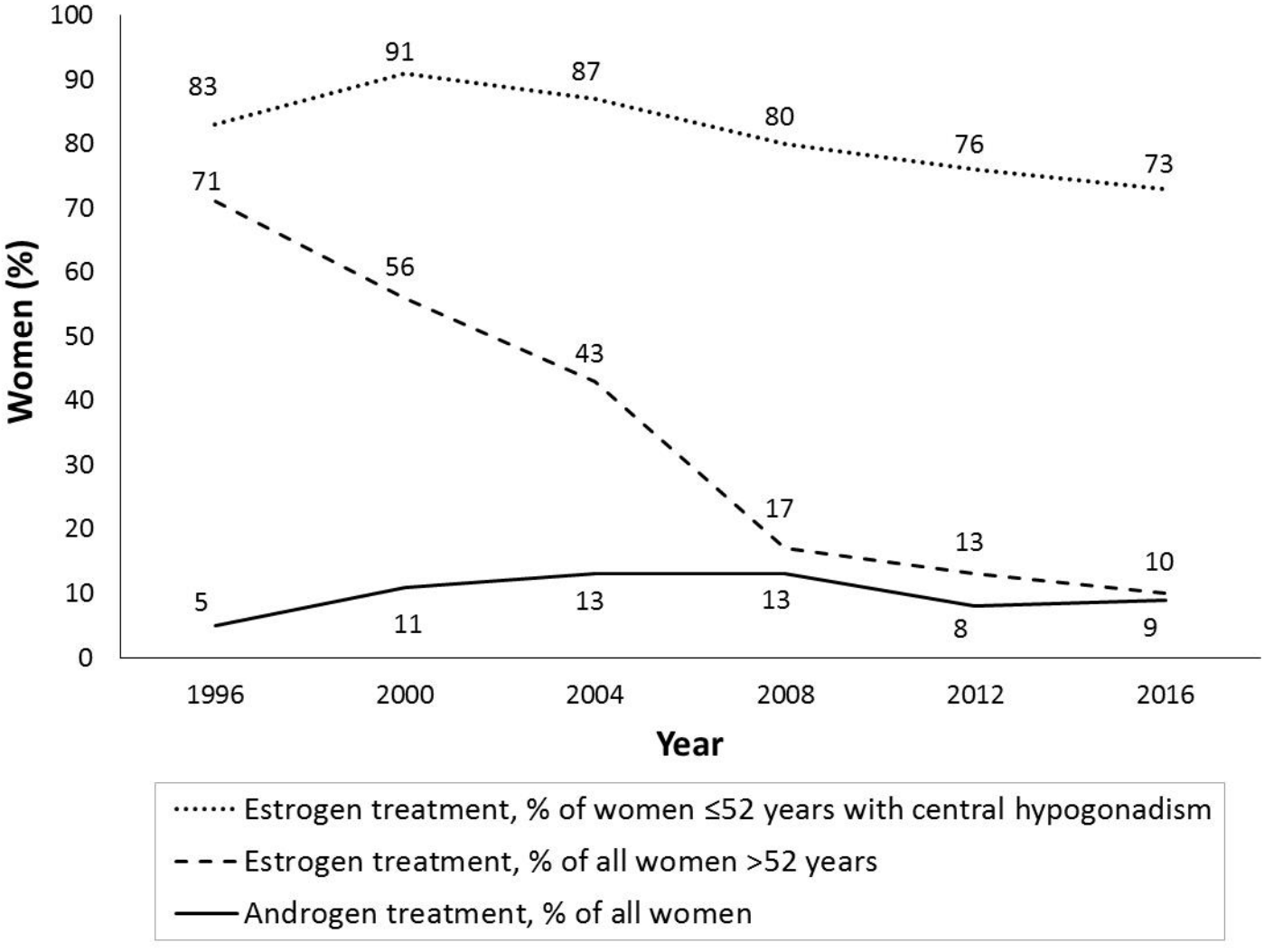
[b] LH/FSH deficiency (central hypogonadism) and estrogen treatment at the time of measurement.

9. Figure legends

Fig. 1 Age distribution of the 184 women with hypopituitarism at the time of the baseline visit (i.e., at the start of GH therapy.

Fig. 2 Estrogen and androgen treatment over time. The proportion (percentage) of women with hypopituitarism who received treatment in the year 1996, 2000, 2004, 2008, 2012 and 2016 was recorded. The age groups (≤ or > 52 years) were updated for each year of assessment.


Women (n)
30
25
20
15
10
5
0
17-19
20-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75-77
Age at the baseline visit (years)


100
90
80
70
60
50
40
30
20
10
0
Women (%)
83
91
87
80
76
73
71
56
43
17
13
10
5
11
13
13
8
9
1996
2000
2004
2008
2012
2016
Year
Estrogen treatment, % of women ≤52 years with central hypogonadism
Estrogen treatment, % of all women >52 years
Androgen treatment, % of all women