

## Optimal feminizing hormone treatment in transgender people

Glintborg, Dorte; T'Sjoen, Guy; Ravn, Pernille; Andersen, Marianne Skovsager

*Published in:*  
European Journal of Endocrinology

*DOI:*  
10.1530/EJE-21-0059

*Publication date:*  
2021

*Document version:*  
Accepted manuscript

*Citation for published version (APA):*  
Glintborg, D., T'Sjoen, G., Ravn, P., & Andersen, M. S. (2021). Optimal feminizing hormone treatment in transgender people. *European Journal of Endocrinology*, 185(2), R49-R63. <https://doi.org/10.1530/EJE-21-0059>

Go to publication entry in University of Southern Denmark's Research Portal

### Terms of use

This work is brought to you by the University of Southern Denmark.  
Unless otherwise specified it has been shared according to the terms for self-archiving.  
If no other license is stated, these terms apply:

- You may download this work for personal use only.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying this open access version

If you believe that this document breaches copyright please contact us providing details and we will investigate your claim.  
Please direct all enquiries to [puresupport@bib.sdu.dk](mailto:puresupport@bib.sdu.dk)

1 **Optimal feminizing hormone treatment in transgender people**

2 Dorte Glintborg (1), Guy T'Sjoen (2), Pernille Ravn (3), Marianne Skovsager Andersen (1)

3

4 (1) Department of Endocrinology, Odense University Hospital, Odense, Denmark

5 (2) Department of Endocrinology and Center for Sexology and Gender, Ghent University

6 Hospital, Ghent, Belgium

7 (3) Department of Gynaecology and Obstetrics, Odense University Hospital, Odense, Denmark

8

9 **Corresponding author:**

10 Dorte Glintborg

11 Department of Endocrinology, Odense University Hospital

12 [dorte.glintborg@rsyd.dk](mailto:dorte.glintborg@rsyd.dk)

13 +45 26 40 76 97

14

15 **Key words:** transgender, estrogen, cyproterone acetate, GnRH, spironolactone

16 **Short title:** Feminizing treatment in transgender women

17 **Word count:** 4500

18

19 **Funding:** None

20 **Disclosure:** Nothing to declare.

21

22 **Abstract**

23 Transgender women are assigned male at birth, but identify as women. The incidence of gender dysphoria is  
24 estimated to be around 1% of the population. Gender dysphoria may be associated with depression and low  
25 quality of life, which in most cases improves during gender affirming hormonal treatment (GAHT).

26 Feminizing hormonal treatment for transgender women or gender non-binary people typically includes  
27 natural estrogen (estradiol). Additional testosterone-blocking treatment is often needed to ensure suppression  
28 of the pituitary gonadal axis and may include cyproterone acetate, a gonadotropin releasing hormone agonist  
29 (GnRH-a) or spironolactone. The health risks of cyproterone acetate as anti-androgen treatment are debated  
30 and randomized protocols with other anti-androgen treatments are requested. Orchiectomy is performed in  
31 some transgender women after various duration of GAHT. Currently, natural progesterone is not  
32 recommended as part of GAHT due to limited knowledge on the balance between risks and benefits.

33 In the present article we discuss evidence regarding established and upcoming feminizing treatment for adult  
34 transgender women or for gender non-binary people seeking feminization. Data on study populations with  
35 transgender women are put into a wider context of literature regarding effects of sex steroid hormones in  
36 cisgender study populations. Relevant follow up and monitoring during feminizing treatment is debated. The  
37 review has special focus on the pharmacotherapy of feminizing hormonal therapy.

38

## 39 **Introduction**

40 The term transgender is used to describe individuals, whose gender identity differs from the assigned gender  
41 at birth. Transgender women are persons assigned male at birth, but who identify as women. In a recent  
42 European study, 0.7- 1.1% of the general population reported incongruent gender identity (1).

43 In transgender persons, about one out of three identifies as gender non-binary (2). Gender non-binary is an  
44 umbrella term for gender identities that are neither male nor female—identities that are outside the gender  
45 binary (2). Gender non-binary people may also seek feminization. Medical doctors are needed to prescribe  
46 hormone therapy in most of Europe, United States, and Canada, but gender affirming hormonal therapy  
47 (GAHT) may also be obtained from unofficial sources. In many countries, GAHT is predominantly  
48 prescribed by centers with a special interest in transgender health, also called gender teams. These  
49 multidisciplinary gender teams initiate and offer psychological support before and during transition and  
50 prescribe GAHT. Furthermore, the gender teams help to coordinate referrals for gender affirming surgery  
51 and involvement of other specialists (dermatology, plastic surgery, urology, gynecology,  
52 otorhinolaryngology etc.). Current guidelines and position statements describe the initial assessment of  
53 transgender women (3, 4).

54 GAHT in transgender women aims for development and maintenance of secondary feminine characteristics  
55 and suppression of secondary masculine characteristics. Feminizing hormonal treatment usually includes  
56 natural estrogen (estradiol, E2) alone or in combination with testosterone-blocking treatment (1). E2 is  
57 administered transdermally, orally, or as injections (5). Anti-androgen treatment may include cyproterone  
58 acetate (CPA), a gonadotropin releasing hormone agonist (GnRH-a) or spironolactone (5). Anti-androgen  
59 treatment is discontinued if the patient undergoes orchiectomy or if estrogen-only treatment has proven  
60 sufficient.

61 In the present review, we discuss evidence regarding established and upcoming methods for feminizing  
62 treatment in adult transgender women and gender non-binary women with a wish for feminization. We put  
63 available data on GAHT into a wider context of literature regarding effects of sex hormones in cisgender

64 study populations. The review has special focus on the pharmacotherapy of feminizing hormonal  
65 therapy.

66

## 67 **Methods**

68 The paper was designed as a narrative review regarding GAHT in adult transgender women. We searched for  
69 available clinical trials and placebo-controlled trials in study cohorts of adult transgender women published  
70 until December 2020 in PubMed. We performed a search using the term: “transgender” in combination with  
71 one of the terms: placebo controlled trial, clinical trial, medicine prescription, drug prescription, gender  
72 affirming hormonal therapy. The search term transgender was replaced with trans-sexualism, gender  
73 incongruence, trans female, and trans woman. We also searched for papers including each identified  
74 treatment modality: estrogen, estradiol, spironolactone, anti-androgen, androgen blocker, androgen  
75 antagonist, cyproterone acetate, cyproterone, flutamide, finasteride, gonadorelin, GnRH-a, progestogen,  
76 progesterone, progestin, thus including all hormonal feminizing treatments, in combination with one of the  
77 search terms for transgender. Further relevant studies were identified by cross search from reference lists in  
78 identified studies. We excluded studies regarding treatment of children/teenagers <18 years (puberty  
79 blockers) and studies focusing on surgical procedures. Dermatologic treatment of hirsutism is covered in  
80 other recent reviews (6, 7) and is not covered in this paper. Lifestyle intervention, treatment of weight  
81 problems, and gender affirming surgical interventions are considered outside the scope of this paper. Datasets  
82 on hormone treatment in gender non-binary people are lacking and therefore this is not specifically  
83 addressed, although we acknowledge that some papers in this review may include gender non-binary persons  
84 seeking feminizing treatment. In case of limited literature in transgender study populations, we included and  
85 discussed studies performed in cisgender study populations. Furthermore, knowledge regarding effects of sex  
86 hormones in cisgender study populations was discussed in the context of transgender health.

87

## 88 **Gender affirming hormonal treatment (GAHT)**

89 In transgender women, the desired effect of GAHT is development of secondary female characteristics  
90 including breast growth and a female body composition. Anti-androgen treatment may be needed to ensure  
91 full suppression of the pituitary-gonadal axis and suppression of secondary male characteristics such as  
92 terminal body hair growth.

93 **Estrogen treatment**

94 **Background:** The most important endogenous estrogens include 17 $\beta$ -estradiol (E2), estrone (E1) and estriol  
95 (E3), where E2 is found at the highest concentration and is the most potent estrogen. E2 acts at the nuclear  
96 estrogen receptors  $\alpha$  and  $\beta$ , which leads to different transcriptional effects. Apart from genomic effects, E2  
97 can activate non-genomic G-coupled estrogen receptors (8). The E2 level in adult cisgender men is around  
98 0.1 nmol/l compared to 0.4 -0.5 nmol/l in premenopausal women at mid-cycle (9). In cisgender men, 75% E2  
99 is produced by peripheral aromatization of testosterone (9). The biological roles of E2 in males include  
100 endothelial repair and regeneration, decrease of body fat, preservation of bone health, and increase of growth  
101 hormone secretion (9, 10).

102 Estrogen can be given synthetically as ethinyloestradiol (oral contraceptives) or naturally as E2. Pro-  
103 coagulant side effects of synthetic estrogens are well described (11), which makes treatment with  
104 ethinylestradiol obsolete for GAHT. E2 is considered first line drug for GAHT in transgender women. E2  
105 can be applied orally, trans-dermally or as intramuscular injections. Table 1 gives an overview of the  
106 different treatment regimens of E2. Oral E2 is metabolized in the intestines and liver into E1 and estrogen  
107 conjugates before entering the circulation (first pass metabolism)(12). As a result, the ratio of circulating  
108 E1/E2 is 5/1 after oral E2 compared to 1/1 after transdermal E2. Transdermal E2 gives a more constant, non-  
109 fluctuating serum E2 without circulating estrogen metabolites, which may be advantageous in terms of  
110 cardio-metabolic side effects (13). According to current treatment guidelines, transdermal E2 is considered  
111 first line treatment in transgender women >40 years (14-16). Intramuscular E2 is associated with a peak in  
112 E2 lasting for about two weeks and reaching values up to six times higher than average E2 concentration in  
113 cisgender women (17). Such high serum E2 levels may potentially be associated with thromboembolic  
114 events. In most European countries, intramuscular injections are not available. Buccal E2 can be used for  
115 treatment of hot flashes in postmenopausal women (18), however, use of buccal E2 in transgender women  
116 may be limited by lower concentrations and fluctuating E2 levels (19). Studies regarding feminizing effects  
117 of GAHT most often evaluated breast growth, whereas other outcomes are less evaluated. Studies comparing  
118 efficacy depending on route of E2 application in transgender women are sparse (20), and are discussed

119 further below. Most studies applied combined treatment regimens, which makes individual effect of different  
120 estrogen preparations and antiandrogen drugs difficult to evaluate.

121

## 122 **Anti-androgen treatment**

123 The most commonly used antiandrogen treatments are CPA, GnRH-a, and spironolactone. Anti-androgen  
124 treatment is for many a cornerstone of feminizing treatment. E2 treatment in transgender women ensures  
125 serum E2 within reference interval for cisgender women, but the pituitary-gonadal axis will often not be  
126 sufficiently suppressed by E2 treatment alone. Testosterone is an important masculinizing and anabolic  
127 hormone. The masculinizing effects of testosterone include stimulation of the male reproductive tract and  
128 development of secondary sex characteristics (e.g. terminal hair growth), whereas the anabolic effects of  
129 testosterone include stimulation of somatic tissue, such as muscle. Testosterone acts as a prohormone and is  
130 converted to the biologically active derivate dihydrotestosterone (DHT) by the enzyme  $5\alpha$ -reductase or to E2  
131 by aromatase. Aromatization of androgens to estrogens occurs in adipose tissue muscle, bone and brain (9).  
132 Many of the masculinizing effects of endogenous testosterone until initiation of feminizing treatment during  
133 puberty and adult life will not be reverted despite partially or completely suppression of androgen levels.  
134 Therefore, in most cases, additional treatment is needed, which may include voice training, surgical  
135 intervention on the vocal cords, laser treatment of terminal hair growth and maybe facial surgery (1).  
136 Importantly, anti-androgen treatment will result in testicular atrophy and azoospermia within few months.  
137 After longer treatment duration (2-3 years), the decrease in fertility is considered, at least partially,  
138 irreversible, therefore sperm cryopreservation should be carefully discussed before prescription of anti-  
139 androgen treatment (21, 22). In the case of orchiectomy, anti-androgen treatment can be stopped and spare  
140 the patient from side effects of anti-androgen treatment. The timing of orchiectomy will very much depend  
141 on local traditions including the possibility for genital reconstruction surgery.  
142 The choice of anti-androgen treatment will very much depend on national availability, pricing and financing  
143 of drugs (1). In Europe, the most commonly prescribed androgen lowering medication for feminization is  
144 CPA. Spironolactone is commonly prescribed in the US where CPA is not available (1). GnRH-a are



145 provided free of charge to transgender women by the National Health Service in the United Kingdom,  
146 whereas for example in Belgium, Denmark, and Australia, GnRH-a is provided by the hospital for puberty  
147 suppression only (23).

148 The mechanism for testosterone suppression differs between different anti-androgen treatments. In overview,  
149 anti-androgen treatments include androgen receptor antagonists (spironolactone and flutamide), whereas  
150 GnRH-a and progestogens suppress the hypothalamic pituitary gonadal axis. CPA has dual action on the  
151 androgen receptor and on the hypothalamic pituitary gonadal axis. 5- $\alpha$  reductase inhibitors block the  
152 conversion of testosterone to dihydrotestosterone.

153 Feminization and androgen suppression is the primary goal of anti-androgen treatment as part of GAHT. One  
154 Cochrane review in transgender women found no study regarding efficacy and safety of hormone therapy  
155 with antiandrogens or E2 alone, or in combination (20). One recent systematic review found four studies  
156 regarding the effects of different anti-androgen treatment modalities on testosterone levels in transgender  
157 women (23). The authors concluded that addition of CPA, GnRH-a and progestin may be more effective than  
158 spironolactone or estradiol alone at suppressing the serum total testosterone concentration (23). The authors  
159 found no eligible studies regarding effects of antiandrogens on breast development or facial and body hair  
160 reduction (23). Serum levels of testosterone may not be meaningful endpoints for feminization especially for  
161 androgen receptor antagonists (23). The recent review by Angus *et al* (23) did not include a discussion  
162 regarding safety and dosage of individual anti-androgen treatment modalities, and these issues will be further  
163 discussed in the present review.

164

### 165 **Cyproterone acetate (CPA)**

166 CPA inhibits the testosterone receptor and acts as synthetic progesterone (progestin), which results in  
167 suppression of the hypothalamic-pituitary-gonadal axis. CPA is part of oral contraceptives with anti-  
168 androgen effect (G03HB01, containing 2 mg CPA per tablet), which can be prescribed as second line oral  
169 contraceptives to treat hirsutism in cisgender women. For transgender women, CPA has the benefit of being  
170 relatively cheap and CPA is administered orally in contrast to GnRH-a (1). After oral ingestion, the maximal

171 plasma concentration is reached after around three hours and the turn over time is slow with plasma half time  
172 of 2-3 days. Therefore, CPA can also be administered every 2<sup>nd</sup> or even every 3<sup>rd</sup> day.

173 CPA is a strong inhibitor of serum testosterone. A recent paper found significantly lower total testosterone  
174 concentrations (0.8 nmol/L (0.6-1.20 nmol/L)) during CPA in transgender women compared to testosterone  
175 levels during spironolactone (2.0 nmol/L (0.9-9.4 nmol/L) and E2 alone (10.5 nmol/L (4.9-17.2 nmol/L)  
176 (24)). The median daily CPA dosage in the study was 50 mg (24). The progestin effect of CPA may improve  
177 breast development (1). However, as mentioned above, no data are available regarding the feminizing effect  
178 of CPA alone in transgender women (23).

179 Several reservations may apply to the use of CPA. Observational studies in transgender women reported  
180 adverse lipid status (low HDL) during CPA (25) (26) and insulin resistance tended to increase during  
181 feminizing treatment including CPA (27), but findings could in part be explained by changed body  
182 composition with higher body weight and higher waist hip ratio (27). Prolactin levels increased during CPA  
183 (28, 29), but serum prolactin levels normalized after stopping CPA (28). Prolactin is also an adipokine, and  
184 high prolactin levels outside reference interval could infer higher metabolic risk (30). A possible association  
185 between high prolactin and breast cancer is undetermined (31). The risk of breast cancer increases during  
186 feminizing treatment, but most tumors are estrogen and progesterone receptor positive (32). The known  
187 association between CPA therapy and development of meningiomas (33) depends on cumulated dose (33),  
188 thus international health authorities recommend that CPA should be used with caution to avoid long-term  
189 risk of meningioma (34). At present, nine cases of meningioma have been described in transgender women,  
190 which is an elevated relative risk, but still very low absolute risk (35). In many centers, the dosage of CPA  
191 has been 25-50 mg/day by initiation of feminizing treatment, but in the future the starting dosage of CPA  
192 could be reduced to 12.5 mg/day and further down-titration of CPA can be considered after 6-12 months.  
193 CPA 10 mg/day should be administered for no more than two years to keep below the maximal cumulative  
194 dose. Alternative anti-androgen use and earlier orchiectomy should be considered in order to avoid  
195 meningiomas during CPA. Furthermore, healthy lifestyle should be supported to avoid weight gain and  
196 adverse metabolic profile during CPA treatment.

197

198 **Spirolactone**

199 Spirolactone is a non-selective mineralocorticoid, and is an androgen and progesterone receptor  
200 antagonist. Spirolactone blocks the binding of dihydrotestosterone to its androgen receptor, thereby  
201 inhibiting androgen effects (24). The binding capacity of spironolactone to the androgen receptor is weaker  
202 than CPA (24). Spirolactone also acts as an inhibitor of  $17\alpha$ -hydroxylase and  $17,20$ -lyase (enzymes in the  
203 testosterone biosynthetic pathway), which lowers testosterone to a small degree (24). The use of  
204 spironolactone for treatment of hirsutism in cisgender women is well described and spironolactone can be  
205 given as part of oral contraceptives as drospirinone (4<sup>th</sup> generation oral contraceptive)(36).  
206 In transgender women, spironolactone is administered orally as tablets in 25 mg, 50 mg, or 100 mg doses.  
207 Few studies evaluated the feminizing effects of spironolactone treatment in transgender women. In a recent  
208 non-randomized Australian study (38 transgender women treated with spironolactone), the average  
209 prescribed dosage of spironolactone was 100 mg (interquartile range) (87.5–200 mg). Serum testosterone  
210 levels during spironolactone treatment were significantly higher compared to CPA (2.0 vs. 0.8 nmol/L),  
211 however, data regarding feminizing physical characteristics and treatment satisfaction were not available (24,  
212 26). As discussed by the authors, the mechanisms of actions differ between CPA and spironolactone and  
213 level of total testosterone concentration may not be an applicable marker of feminization (24).  
214 Several studies supported that spironolactone could improve metabolic risk compared to CPA. HDL levels  
215 increased (25) during spironolactone without any significant changes in prolactin (25, 26, 37) and potassium  
216 levels (26, 38).

217

218 **GnRH-a**

219 GnRH-a inhibit the pituitary gonadal axis and lead to suppressed gonadal sex-hormone levels, whereas  
220 adrenal androgen production is kept intact. In children, GnRH-a is used for treatment of central precocious  
221 puberty. In adults, GnRH-a is applied as part of fertility treatment, treatment of endometriosis, and prostate  
222 cancer. GnRH-a is usually administered by depot injections, and the cost of treatment is relatively high. In  
223 many countries, GnRH-a is commonly prescribed to suppress endogenous puberty in transgender  
224 adolescents, whereas GnRH-a treatment is not commonly applied for treatment in adult transgender women

225 (1) due to the high cost and other available treatments (1). As a result, the use of GnRH-a has mainly been  
226 studied in adolescent study populations. One study in transgender girls reported effective gonadal  
227 suppression after three months GnRH-a treatment resulting in nearly undetectable gonadotropins levels and  
228 decreased testosterone from 9.1 nmol/L to 1.0 nmol/L (39). A main concern is long-term health  
229 consequences of gonadal suppression (40). Bone mineral density Z-scores remained below zero in  
230 transgender girls three years after treatment with combined GnRH-a and E2 (41). We are not aware of long-  
231 term studies on fracture risk following suppression of puberty. Limited data are available in adult  
232 transgender female study populations regarding study outcomes of previous puberty blocking such as  
233 cardiovascular risk. A Trans Youth Care Research Network was established in the US with the aim to  
234 perform a longitudinal observational study in young transgender individuals starting puberty blockers  
235 compared to individuals starting GAHT without GnRH-a (42). Data from this study cohort showed that  
236 transgender women treated with GnRH-a + estrogen needed lower doses of estrogen to achieve desired  
237 physiologic changes compared to transgender women not using GnRH-a (43). However, the number of  
238 transgender women treated with GNRH-a was so far limited to only six and spironolactone was used as an  
239 androgen blocker in the comparison group, which could have affected study outcomes (43). Administration  
240 of GnRH-a in early puberty will lead to underdevelopment of the penis, which can compromise future  
241 vaginoplasty (44). Furthermore, termination of puberty will lead to underdeveloped testes and semen  
242 production, which will compromise options for fertility preservation (45).

243

#### 244 **5 $\alpha$ -reductase inhibitors**

245 Finasteride and dutasteride are 5 $\alpha$ -reductase inhibitors, which inhibit the conversion of testosterone to the  
246 more active dihydrotestosterone. Furthermore, 5 $\alpha$ -reductase inhibitors block the conversion of progesterone  
247 to dihydroprogesterone and deoxycorticosterone to dihydrodeoxycorticosterone (46). The use of 5 $\alpha$ -  
248 reductase inhibitors is prescribed in cisgender men for treatment of benign prostate hypertrophy and  
249 sometimes for treatment of androgenic hair loss, whereas use of 5 $\alpha$ -reductase inhibitors in transgender  
250 women is controversial (46). Transgender women may request 5 $\alpha$ -reductase inhibitors to improve anti-

251 androgen effects of feminizing treatment, but no clinical studies supported their use. Especially when  
252 testosterone levels are already suppressed, as seen during CPA or spironolactone treatment, the benefit of 5 $\alpha$ -  
253 reductase inhibitors will probably be negligible. As recently discussed, testosterone levels could increase  
254 during treatment with 5 $\alpha$ -reductase inhibitors (46, 47). We are not aware of studies in transgender women  
255 regarding the effect of 5 $\alpha$ -reductase inhibitors on secondary female characteristics. In conclusion, treatment  
256 with 5 $\alpha$ - reductase inhibitors in transgender women is considered to be of no clinical benefit and is therefore  
257 not recommended.

258

### 259 **Flutamide**

260 Flutamide acts as a selective antagonist of the androgen receptor (AR) and is used for treatment of prostate  
261 cancer. Testosterone levels are unchanged during flutamide treatment and due to risk of hepatotoxic side  
262 effects, flutamide it not recommended for GAHT (1).

263

### 264 **Progesterone**

265 In a menstrual cycle, progesterone levels surge after ovulation and measurement of serum progesterone in  
266 late menstrual cycle is applied to determine ovulatory cycles. The stimulatory effect of progesterone on  
267 female breast development is well described and progesterone promotes alveologensis and ductal side  
268 branching (48). Progesterone (progestogen) therapy can be prescribed as the natural hormone or synthetic as  
269 progestins. Natural progesterone is used as part of fertility treatment and progestins are used in oral  
270 contraceptives.

271 In transgender women, the mechanism for a feminizing effect of progestogens is inhibition of the  
272 hypothalamic-pituitary-gonadal axis and possibly improved breast development. As earlier discussed,  
273 feminizing treatment with CPA imply a considerable progestin effect. Therefore, reduction of CPA dosage to  
274 a minimum may lead to higher request for additional progesterone treatment. Breast development during  
275 progesterone treatment in transgender women has been investigated as part of lactation induction, where  
276 transgender women were treated with high dosage progesterone and domperidone on top of usual GAHT

277 (49). GAHT treatment protocols using medications with progestational properties did not result in a  
278 difference in the request for mammoplasty compared to treatment protocols without progestins (50). Due to  
279 limited evidence regarding breast development, progesterone treatment is currently not recommended in  
280 guidelines (51, 52).

281 The risk of side effects during progesterone treatment is debated. Information regarding the proliferative/  
282 anti-proliferative effects of progesterone in breast cancer is conflicting (48). According to a recent review in  
283 transgender women, half of diagnosed breast cancers were hormone sensitive with positive progesterone  
284 receptor status in five of 14 tested transgender women (53). Natural progesterone treatment may have fewer  
285 adverse effects on breast cancer risk than progestin (54). Mental health could be associated with  
286 progesterone/ estradiol levels (55, 56). Low luteal phase progesterone levels were associated with the peri-  
287 menstrual-syndrome in cisgender women (57). Progestin treatment was associated higher risk of depression  
288 (58), whereas progesterone treatment decreased postpartum depression (59). Whether the progesterone/  
289 estradiol ratio is associated with mental health in transgender women is undetermined.

290 The risk of VTE is considered to be increased during progestogen treatment (60). Progestogens affect the  
291 tissue factor dependent pathway of the coagulation cascade and could increase levels of Protein S and  
292 fibrinogen (60). However, progestogens also affect the concentration of fibrinolytic factors, which questions  
293 the overall effect of progestogens on the turnover of fibrin (60). The effect of natural progesterone on the  
294 hemostatic system is sparsely examined (61). Fluid retention, weight gain and higher blood pressure are well  
295 described side effects of progesterone treatment (62). Progesterone has high affinity for the  
296 mineralocorticoid receptor and acts as a mineralocorticoid receptor antagonist (62, 63). Furthermore,  
297 inhibition of the enzyme 11beta-hydroxysteroid dehydrogenase 2 (11beta-HSD2) by progesterone and its  
298 metabolites results in decreased inactivation of cortisol and hence increased mineralocorticoid receptor  
299 binding by cortisol (62). In contrast, progesterone has been shown to suppress 11beta-HSD1 activity in  
300 cultured human hepatocytes (63), which will decrease cortisol concentrations. Because of these contrasting  
301 effects of progesterone in different tissues, it is clear that only experimental testing can elucidate the *in vivo*  
302 effect of progesterone on mineralocorticoid signaling. We are not aware of studies regarding possible effects

303 of progesterone treatment on blood pressure, renal salt retention, renin/aldosterone ratio and cortisol  
304 metabolites in study populations of transgender women.

305

## 306 **Feminizing effects of GAHT**

307 **Breast development:** Breast development during different treatment regimens in transgender women was  
308 evaluated in few clinical studies. The European Network for the Investigation of Gender Incongruence  
309 (ENIGI) study is an ongoing collaboration of four centers (Amsterdam, Florence, Ghent, and Oslo) (64).  
310 Breast development was investigated in 329 transgender women (average age 28 years) after one year of  
311 feminizing treatment (65). Feminizing treatment included E2 tablets (2 to 6 mg daily), E2 patches (0.05 to  
312 0.1 mg/24 hours twice weekly), or E2 gel (0.75 to 3 mg daily) combined with CPA (10 to 100 mg daily) or  
313 spironolactone (100 to 150 mg daily). Transdermal E2 was advised in transgender women >40 years. The  
314 study reported modest breast development (mean change in breast circumference +3.7 cm), which occurred  
315 primarily within the first 6 months (65). Transdermal E2 resulted in faster increase in breast-chest difference  
316 until 6 months after initializing treatment. However, breast development after one year of feminizing  
317 treatment was comparable between oral and transdermal E2. No clinical or laboratory parameters predicted  
318 breast development (65). Most recently, de Blok *et al.* applied 3D imaging during 3 years of feminizing  
319 treatment in 69 transgender women and reported no associations between increase in breast volume and  
320 treatment regimen, serum E2 levels, age, BMI, and tobacco use (66). These results are in line with a  
321 controlled, retrospective case audit in transgender women seeking mammoplasty after at least 2 years of  
322 feminizing treatment (67). Transgender women were 39 years of age and had been treated with different  
323 hormonal regimens for 10 years in average. The type of estrogen use did not affect the request for  
324 mammoplasty (67).

325

326 **Body composition:** The aim of GAHT is to obtain female body shape with fat redistribution from central to  
327 peripheral fat. A recent meta-analysis included 21 studies and showed that GAHT was associated with  
328 decreased waist-to-hip ratio, a rise in gynoid fat and gain of total fat mass (68). Lean body mass (68) and

329 muscle strength (69) decreased during initiation of GAHT, but muscle strength still remained higher  
330 compared to cisgender women during the first three years of GAHT (69). Interestingly, transgender women  
331 had lower lean body mass and higher fat mass than control males even before initiating GAHT (68). Several  
332 studies supported that GAHT could increase insulin resistance, but long term studies are missing (68).

333

334 **Terminal hair growth (hirsutism).** Quality of life is inversely associated with hirsutism in transgender  
335 women (70), but clinical studies regarding terminal hair growth during GAHT are limited. One study  
336 reported decreased hair growth and sebum production during GAHT and the decrease in hair shaft diameter  
337 reached its maximum at four months (71). Facial hair growth continued during GAHT, but at a slower rate  
338 (71). In accordance, it was reported that more than 90% transgender women had a wish for hair removal  
339 (72).

340

#### 341 **Other treatment effects of GAHT**

342 **Patient reported outcomes, depression and aggression:** The prevalence of depression and low quality of  
343 life is high in transgender study populations (73) and one of the more important aims of GAHT is to improve  
344 quality of life. GAHT is considered beneficial for quality of life and reduction of depression (74), but high  
345 quality data are limited (75). Importantly, suicide rates remain high in transgender persons after GAHT (76).  
346 We are not aware of studies comparing individual treatment regimens regarding patient reported outcomes.  
347 Changes in patient reported outcomes including mental health could be a valuable tool to determine and  
348 validate the effects of GAHT. Depression is more than twice as prevalent in cisgender women compared to  
349 cisgender men (77) and the interaction between estradiol and mental health has been investigated in  
350 cisgender study populations. A national Danish register-based study reported that use of hormonal  
351 contraceptives in cisgender women was followed by increased prescription of antidepressants (58), but all  
352 oral contraceptives contained some form of progesterone. A Swedish register based study found that use of  
353 oral contraceptives was associated with higher risk of suicidal behavior (78). The risk of depression could be  
354 mediated by fluctuating hormone levels as seen during puberty, post-partum, at perimenopause and after



355 initiating oral contraceptives (77, 78). In analogy, in transgender women, the risk of depression could be  
356 highest after initiation of feminizing treatment and if dose reduction of E2 is necessary during ageing or  
357 occurrence of intercurrent disease. Some transgender women may be more susceptible to psychiatric side  
358 effects of estrogen fluctuations (77). Monitoring of depressive symptoms and psychological support could be  
359 warranted during short-term changes in feminizing treatment regimen, whereas long-term stable treatment  
360 seems safer. Fluctuations of testosterone levels could also affect psychological wellbeing in transgender  
361 women in line with the findings in cisgender women, where irritability during the premenstrual phase was  
362 associated with testosterone levels (79). However, in long-term studies, testosterone levels were not  
363 associated with aggression in transgender study populations (80, 81).

364

365 **Sexual health:** In a questionnaire-based cross-sectional study in 214 transgender women, 62% reported  
366 decreased sexual desire after feminizing treatment and 73% never or rarely experienced spontaneous or  
367 responsive sexual desire (82). Four to six years after entering the ENIGI study, 26% of the transgender  
368 women reported difficulties initiating and seeking sexual contact and 28% had difficulties achieving an  
369 orgasm (83). There were no significant differences in study outcomes between participants with or without  
370 intentions for genital surgery (83).

371

372 **Arterial cardiovascular disease (CVD):** Epidemiological studies in transgender women reported increased  
373 risk of acute myocardial infarction and stroke during feminizing treatment, whereas long-term, controlled  
374 studies regarding feminizing treatment and risk of arterial CVD are lacking (84). In contrast, a systematic  
375 review and meta-analysis of cardiovascular outcomes in transgender individuals did not find an increased  
376 risk of myocardial infarction or stroke in transgender women, owing to lack of reported outcomes from 29  
377 eligible studies (85). Feminizing hormone therapy was associated with increased serum triglyceride levels of  
378 31.9 mg/dL (95% CI, 3.9 to 59.9) in transgender women treated for >24 months with no changes in serum  
379 low-density lipoprotein or high-density lipoprotein (85). Of note, CVD is the main cause of death in  
380 cisgender persons, but in general coronary heart disease occurs years later in women compared to men (86).  
381 Premenopausal women are relatively protected against arterial CVD compared to age-matched men and high

382 E2 levels were negatively associated to CVD in postmenopausal women (86). These findings suggest that  
383 endogenous and exogenous estrogens influence the risk of CVD in cisgender women. Findings regarding  
384 higher risk of acute myocardial infarction and stroke during feminizing treatment confirm that CVD risk in  
385 transgender women is influenced by the known risk factors such as high BMI, smoking, sedentary life style,  
386 hypertension, hypercholesterolemia or type 2 diabetes, but also the ‘natal sex atheroma burden’ (84).  
387 Cisgender men will tend to have a larger ‘atheroma burden’ at a given age compared to cisgender women.  
388 Therefore, the age of initiation of feminizing treatment in transgender women is important regarding the  
389 duration of exposure to potential risk factors. Furthermore, age and timing are important with respect to  
390 estrogen therapy, as estrogens may be vasoprotective in women without atherosclerosis as opposed to  
391 women with later stages of atherosclerosis (84). Hypertension is an important risk factor for CVD, which  
392 may be relatively easily modified (86), and E2 protected against hypertension in experimental animal studies  
393 (87).

394

395 **Venous thromboembolism (VTE).** Risk of VTE occurrence in transgender women is likely increased given  
396 the known prothrombotic actions of estrogen (84). In accordance, the incidence of VTE was increased in  
397 transgender women with 2- and 8-year risk differences of 4.1 (95% CI, 1.6 - 6.7) and 16.7 (6.4 - 27.5) per  
398 1000 persons relative to cisgender men and 3.4 (1.1 - 5.6) and 13.7 (4.1 - 22.7) relative to cisgender women  
399 (88). Measurement of coagulation markers confirmed procoagulant changes during initiation of GAHT (89).  
400 Most transgender women need E2 therapy life-long and ageing is a major risk factor for VTE development  
401 (90, 91). Other risk factors for VTE include BMI >25 kg/m<sup>2</sup>, genetic factors and previous VTE (90, 91). The  
402 route of estrogen administration affects the risk of VTE (89, 91). Oral E2 changes hemostatic variables in a  
403 pro-thrombotic direction in contrast to transdermal E2, which was similar to placebo in a recent meta-  
404 analysis (91). Hepatic first-pass effect of oral E2 negatively impacts the synthesis of coagulation proteins,  
405 but other factors play a role (91, 92). At present, oral E2 is not recommended in transgender women with  
406 high risk of VTE and a change to dermal E2 administration should be discussed around the age of 40 years in  
407 all transgender women (1). Adding synthetic progesterone, including CPA, to E2 therapy further increases  
408 the risk of VTE (see below)(91). Anticoagulation therapy following a thrombotic event in transgender

409 women can be considered (1), but there are no long-term studies to guide GAHT in high risk transgender  
410 women and following a thrombotic event.

411

412 **Bone health:** Sex hormones are essential for osteoblast function and eugonadal men and premenopausal  
413 women are relatively protected against osteoporosis. Testosterone levels will decrease during feminizing  
414 treatment, but sufficient treatment with E2 could maintain bone health (93). A recent meta-analysis included  
415 13 studies (392 transgender women) (94). Bone mineral density at the lumbar spine significantly increased  
416 after initiation of feminizing treatment at 12 months (0.04 g/cm<sup>2</sup>; 95% confidence interval 0.03–0.06 g/cm<sup>2</sup>)  
417 and at 24 months (0.06 g/cm<sup>2</sup>; 0.04–0.08 g/cm<sup>2</sup>), which is in the range considered clinically significant (94).  
418 Hip bone mineral density was unchanged (94). The review included studies until 2015 and various estrogen  
419 regimens were applied, which could have affected study results (94). More recently, the ENIGI study  
420 addressed bone turnover markers during a contemporary E2 regimen in 121 transgender women (95). Bone  
421 resorption markers decreased by 10-11% after one year of treatment, which supported protected bone health  
422 (95). One recent study reported higher fracture risk in older transgender women (>50 years) compared to age  
423 matched reference cisgender men, but fracture risk resembled age-matched cisgender women (96). However,  
424 transgender women aged <50 years tended to have a higher fracture risk compared with age-matched  
425 reference cisgender women (96). More prospective data on bone mineral density and fractures in transgender  
426 women are awaited. Importantly, a high percentage of low bone mineral density and hypovitaminosis D was  
427 found prior to GAHT (97). Therefore, evaluation of bone mineral density and 25OH vitamin D before start  
428 of feminizing treatment may be considered in high risk individuals (93, 94). It is important to recognize that  
429 suboptimal medicine compliance in transgender women is associated with low bone mass (97).

430

431 **Cancer risk:** GAHT could affect the risk of hormone sensitive cancer types including breast cancer and  
432 prostate cancer. Furthermore, gender difference is described for several other cancer types in cisgender  
433 people, which suggest an impact of sex hormones. In a recent register based study, cancer diagnosis at later  
434 stages in transgender persons and worse survival for many cancer types was partly explained through  
435 existing barriers to access the healthcare system (98).

436 Breast tissue has estrogen receptors and the risk of breast cancer is higher in cisgender women compared to  
437 cisgender men. Incidence rates of breast cancer in transgender women were lower than in cisgender women  
438 (incidence ratio 0.3) in a recent retrospective Dutch study of 2260 transgender women (median duration of  
439 feminizing treatment, 13 years)(32). The risk of breast cancer increased towards cisgender female levels  
440 during feminizing treatment and the characteristics of breast cancer resembled a female pattern (32, 99).  
441 These results suggest that breast cancer screening guidelines for cisgender women are sufficient for  
442 transgender women on feminizing treatment (32). The study included the whole spectrum of estrogen  
443 treatments and data could not be split up into subgroups of treatment modalities (32). The median age at  
444 breast cancer diagnosis was 50 years (interquartile range 43-55 years). However, a few breast cancer cases  
445 were diagnosed at age 30 years (32), which indicates that transgender women at particular risk (such as  
446 BRCA positive persons) should attend specific screening programs in accordance with those for cisgender  
447 women (99).

448 Prostate cancer is affected by testosterone levels and data support that antiandrogen treatment in transgender  
449 women results in much lower risk of prostate cancer (standardized incidence ratio 0.20, 95% confidence  
450 interval 0.08-0.42)(100). However, presence of estrogen receptor  $\alpha$  cells in a case report of prostate cancer  
451 raised concern for a possible contributing role of exogenous estrogen therapy in tumorigenesis (101).

452 Colorectal cancer is more prevalent in men compared to women. In postmenopausal women, E2 replacement  
453 therapy and consumption of soy reduced the risk of colorectal cancer (102). The protective effect of E2 on  
454 colorectal cancer is mediated by the estrogen receptor subtype  $\beta$  (102). The putative protective effect of  
455 estrogen therapy on the risk of colon cancer in transgender women is undetermined.

456 Esophageal adenocarcinoma has a male to female ratio of 9:1 and the time of diagnosis is postponed for a  
457 median of 16 years in women compared to men (103). This suggests that estrogens may protect and/or  
458 testosterone exposure may increase risk of esophageal adenocarcinoma. However, men with higher  
459 testosterone levels had significantly lower risk of esophageal adenocarcinoma and E2 levels were not  
460 associated with cancer risk (104). Age, BMI and smoking are important risk factors for esophageal  
461 adenocarcinoma (103) and several other cancer types.

462 Obesity and smoking are relative contraindications for GAHT and lifestyle intervention is often part of good  
463 clinical practice of transgender care. Therefore, the individual role of exogenous estrogen for cancer risk in  
464 transgender women will be difficult to determine.

465

## 466 **Monitoring GAHT in transgender care**

467 Objective measurement of breast development (breast-chest difference or 3D imaging) may not be routinely  
468 performed in the clinic and more research is needed to determine the best marker for feminization in study  
469 cohorts of transgender women. Instead, serum E2 is often used to monitor feminizing effect of GAHT.

470 According to recent guidelines for hormonal treatment in transgender persons, the goal of feminizing  
471 treatment is to reach a physiologic serum level of E2 and testosterone for similar aged cisgender women i.e.  
472 serum E2 level in the upper follicular range (0.4 –0.6 mmol/L) and a low serum testosterone (3, 4).

473 Unfortunately, there are no general recommendations regarding timing of blood sampling in relation to E2  
474 administration (105). Timing of blood sampling should reflect the average level of E2, which implies that  
475 sampling should be performed halfway between two E2 administrations. Contamination of the blood sample  
476 by dermally applied hormone should be avoided. Ideally, the timing of blood sampling and drug  
477 administration should be similar across different sampling points to ensure that longitudinal hormone results  
478 are minimally influenced by absorption, metabolism, and user-related discrepancies. In daily clinic, this will  
479 be at least challenging or often impossible. Furthermore, the gold standard for E2 measurement, mass  
480 spectrometry, is not widely available. The use of serum E2 as a marker of feminization contrasts studies  
481 reporting no significant association between E2 levels and breast development (65-67). However, serum E2  
482 was measured by different hormone assays and timing of blood sampling after E2 administration was not  
483 standardized, which could have affected study results (65-67). According to Table 1, E1 measurements could  
484 be relevant during oral E2 treatment, but this hypothesis remains to be tested. Recently, polymorphisms of  
485 the estrogen receptor  $\alpha$  gene was associated with gender incongruence in transgender men, whereas no  
486 association was found in transgender women (106). In postmenopausal women, variations in the estrogen

487 receptors affected individual variation in treatment effects of E2 (107) and further studies regarding  
488 variations in the estrogen receptor are requested in transgender study populations.

489 **Contraindications and reservations for E2 treatment in transgender women.**

490 Long term risks regarding cardiovascular health and cancer should be discussed with the patient before  
491 initiating E2 treatment (Figure 1). Clinical and laboratory work-up at baseline should assess BMI, blood  
492 pressure, lipid profile, and HbA1c. BMI and smoking are important modifiable risk factors for  
493 cardiovascular disease and several cancer types. Obesity and smoking could be considered relative  
494 contraindications for GAHT, but cut off levels for BMI are not available. Of course, lifestyle intervention is  
495 considered part of good clinical practice if needed. In these patients, the preferred use of dermal E2 above  
496 the age of 40 years is discussed above. But, overall, feminizing treatment can be considered safe and  
497 prospective metabolic risk screening can follow current guidelines for cisgender persons (108).

498

499 **Conclusion**

500 GAHT for transgender women should be tailored to the individual patient. In normal weight younger persons  
501 the *a priori* general health is usually good and the choice of treatment can be done quite freely. However, as  
502 age, BMI and cardio-metabolic risk factors increase, feminizing treatment should be prescribed under  
503 consideration of risk factors. Lifestyle factors should always be discussed as part of the outpatient  
504 consultation. There is a need for clinical studies exploring the optimal treatment of transgender women.  
505 Overall, feminization treatment can be considered as safe, but hormonal treatment may need adaptations if  
506 health risk factors develops over time. Future studies should add patient reported outcomes including  
507 satisfaction with breast development as these outcomes may not correlate with serum measures of E2 and  
508 testosterone levels.

509

510

511

512

513

514

515

516

517

518

519

520

521

522

523

524

525

526

527

528

529

530

531

532

533

534

535

536

537

538

539

540

541

542

543

544

545

546

547

548

549

550

551

552

553

554

555

556

557

558

559

560

1. T'Sjoen G, Arcelus J, Gooren L, Klink DT, Tangpricha V. Endocrinology of Transgender Medicine. *Endocr Rev.* 2019;40(1):97-117.
2. Burgwal A, Gvianishvili N, Hård V, Kata J, García Nieto I, Orre C, Smiley A, Vidić J, Motmans J. Health disparities between binary and non binary trans people: A community-driven survey. *Int J Transgend.* 2019;20(2-3):218-29.
3. Hembree WC, Cohen-Kettenis PT, Gooren L, Hannema SE, Meyer WJ, Murad MH, Rosenthal SM, Safer JD, Tangpricha V, T'Sjoen GG. Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2017;102(11):3869-903.
4. T'Sjoen G, Arcelus J, De Vries ALC, Fisher AD, Nieder TO, Özer M, Motmans J. European Society for Sexual Medicine Position Statement "Assessment and Hormonal Management in Adolescent and Adult Trans People, With Attention for Sexual Function and Satisfaction". *J Sex Med.* 2020;17(4):570-84.
5. Randolph JF, Jr. Gender-Affirming Hormone Therapy for Transgender Females. *Clin Obstet Gynecol.* 2018;61(4):705-21.
6. Marks DH, Peebles JK, Dommasch E. Hair Reduction for Transgender Persons: What Dermatologists Should Know and How They Can Help. *JAMA Dermatol.* 2019;155(5):525-6.
7. Yeung H, Kahn B, Ly BC, Tangpricha V. Dermatologic Conditions in Transgender Populations. *Endocrinol Metab Clin North Am.* 2019;48(2):429-40.
8. Fardoun M, Dehaini H, Shaito A, Mesmar J, El-Yazbi A, Badran A, Beydoun E, Eid AH. The hypertensive potential of estrogen: An untold story. *Vascul Pharmacol.* 2020;124:106600.
9. Russell N, Grossmann M. MECHANISMS IN ENDOCRINOLOGY: Estradiol as a male hormone. *European journal of endocrinology.* 2019.
10. Smith GI, Yoshino J, Reeds DN, Bradley D, Burrows RE, Heisey HD, Moseley AC, Mittendorfer B. Testosterone and progesterone, but not estradiol, stimulate muscle protein synthesis in postmenopausal women. *J Clin Endocrinol Metab.* 2014;99(1):256-65.
11. Sidelmann JJ, Jespersen J, Andersen LF, Skouby SO. Hormone replacement therapy and hypercoagulability. Results from the Prospective Collaborative Danish Climacteric Study. *Bjog.* 2003;110(6):541-7.
12. Selby P, McGarrigle HH, Peacock M. Comparison of the effects of oral and transdermal oestradiol administration on oestrogen metabolism, protein synthesis, gonadotrophin release, bone turnover and climacteric symptoms in postmenopausal women. *Clin Endocrinol (Oxf).* 1989;30(3):241-9.
13. Streed CG, Jr., Harfouch O, Marvel F, Blumenthal RS, Martin SS, Mukherjee M. Cardiovascular Disease Among Transgender Adults Receiving Hormone Therapy: A Narrative Review. *Ann Intern Med.* 2017;167(4):256-67.
14. Gooren L, Lips P. Conjectures concerning cross-sex hormone treatment of aging transsexual persons. *J Sex Med.* 2014;11(8):2012-9.
15. Gooren LJ, T'Sjoen G. Endocrine treatment of aging transgender people. *Rev Endocr Metab Disord.* 2018;19(3):253-62.
16. Asscheman H, Giltay EJ, Megens JA, de Ronde WP, van Trotsenburg MA, Gooren LJ. A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones. *European journal of endocrinology.* 2011;164(4):635-42.
17. Sierra-Ramírez JA, Lara-Ricalde R, Lujan M, Velázquez-Ramírez N, Godínez-Victoria M, Hernández-Munguía IA, Padilla A, Garza-Flores J. Comparative pharmacokinetics and

561 pharmacodynamics after subcutaneous and intramuscular administration of medroxyprogesterone  
562 acetate (25 mg) and estradiol cypionate (5 mg). *Contraception*. 2011;84(6):565-70.

563 18. Gass MS, Rebar RW, Cuffie-Jackson C, Cedars MI, Lobo RA, Shoupe D, Judd HL,  
564 Buyalos RP, Clisham PR. A short study in the treatment of hot flashes with buccal administration of  
565 17-beta estradiol. *Maturitas*. 2004;49(2):140-7.

566 19. Salehian B, Wang C, Alexander G, Davidson T, McDonald V, Berman N, Dudley RE,  
567 Ziel F, Swerdloff RS. Pharmacokinetics, bioefficacy, and safety of sublingual testosterone  
568 cyclodextrin in hypogonadal men: comparison to testosterone enanthate--a clinical research center  
569 study. *J Clin Endocrinol Metab*. 1995;80(12):3567-75.

570 20. Haupt C, Henke M, Kutschmar A, Hauser B, Baldinger S, Saenz SR, Schreiber G.  
571 Antiandrogen or estradiol treatment or both during hormone therapy in transitioning transgender  
572 women. *Cochrane Database Syst Rev*. 2020;11:Cd013138.

573 21. De Roo C, Tilleman K, T'Sjoen G, De Sutter P. Fertility options in transgender  
574 people. *Int Rev Psychiatry*. 2016;28(1):112-9.

575 22. Vereecke G, Defreyne J, Van Saen D, Collet S, Van Dorpe J, T'Sjoen G, Goossens E.  
576 Characterisation of testicular function and spermatogenesis in transgender women. *Hum Reprod*.  
577 2020.

578 23. Angus LM, Nolan BJ, Zajac JD, Cheung AS. A systematic review of anti-androgens  
579 and feminisation in transgender women. *Clin Endocrinol (Oxf)*. 2020.

580 24. Angus L, Leemaqz S, Ooi O, Cundill P, Silberstein N, Locke P, Zajac JD, Cheung  
581 AS. Cyproterone acetate or spironolactone in lowering testosterone concentrations for transgender  
582 individuals receiving oestradiol therapy. *Endocrine connections*. 2019;8(7):935-40.

583 25. Fung R, Hellstern-Layefsky M, Tastenhoye C, Lega I, Steele L. Differential Effects of  
584 Cyproterone Acetate vs Spironolactone on Serum High-Density Lipoprotein and Prolactin  
585 Concentrations in the Hormonal Treatment of Transgender Women. *J Sex Med*. 2016;13(11):1765-  
586 72.

587 26. Sofer Y, Yaish I, Yaron M, Bach MY, Stern N, Greenman Y. Differential endocrine  
588 and metabolic effects of testosterone suppressive agents in transgender women. *Endocr Pract*.  
589 2020;26(8):883-90.

590 27. Shadid S, Abosi-Appadu K, De Maertelaere AS, Defreyne J, Veldeman L, Holst JJ,  
591 Lapauw B, Vilsbøll T, T'Sjoen G. Effects of Gender-Affirming Hormone Therapy on Insulin  
592 Sensitivity and Incretin Responses in Transgender People. *Diabetes Care*. 2020;43(2):411-7.

593 28. Defreyne J, Nota N, Pereira C, Schreiner T, Fisher AD, den Heijer M, T'Sjoen G.  
594 Transient Elevated Serum Prolactin in Trans Women Is Caused by Cyproterone Acetate Treatment.  
595 *LGBT Health*. 2017;4(5):328-36.

596 29. Nota NM, Dekker M, Klaver M, Wiepjes CM, van Trotsenburg MA, Heijboer AC,  
597 den Heijer M. Prolactin levels during short- and long-term cross-sex hormone treatment: an  
598 observational study in transgender persons. *Andrologia*. 2017;49(6).

599 30. Andersen M, Glintborg D. Metabolic Syndrome in Hyperprolactinemia. *Front Horm*  
600 *Res*. 2018;49:29-47.

601 31. De Hert M, Peuskens J, Sabbe T, Mitchell AJ, Stubbs B, Neven P, Wildiers H,  
602 Detraux J. Relationship between prolactin, breast cancer risk, and antipsychotics in patients with  
603 schizophrenia: a critical review. *Acta Psychiatr Scand*. 2016;133(1):5-22.

604 32. de Blok CJM, Wiepjes CM, Nota NM, van Engelen K, Adank MA, Dreijerink KMA,  
605 Barbé E, Konings I, den Heijer M. Breast cancer risk in transgender people receiving hormone  
606 treatment: nationwide cohort study in the Netherlands. *Bmj*. 2019;365:11652.



- 607 33. Nota NM, Wiepjes CM, de Blok CJM, Gooren LJG, Peerdeman SM, Kreukels BPC,  
608 den Heijer M. The occurrence of benign brain tumours in transgender individuals during cross-sex  
609 hormone treatment. *Brain*. 2018;141(7):2047-54.
- 610 34. [Available from:  
611 [https://www.ema.europa.eu/en/medicines/human/referrals/cyproterone-containing-medicinal-](https://www.ema.europa.eu/en/medicines/human/referrals/cyproterone-containing-medicinal-products)  
612 [products](https://www.ema.europa.eu/en/medicines/human/referrals/cyproterone-containing-medicinal-products).]
- 613 35. Mancini I, Rotilio A, Coati I, Seracchioli R, Martelli V, Meriggiola MC. Presentation  
614 of a meningioma in a transwoman after nine years of cyproterone acetate and estradiol intake: case  
615 report and literature review. *Gynecol Endocrinol*. 2018;34(6):456-9.
- 616 36. Barrionuevo P, Nabhan M, Altayar O, Wang Z, Erwin PJ, Asi N, Martin KA, Murad  
617 MH. Treatment Options for Hirsutism: A Systematic Review and Network Meta-Analysis. *J Clin*  
618 *Endocrinol Metab*. 2018;103(4):1258-64.
- 619 37. Bisson JR, Chan KJ, Safer JD. PROLACTIN LEVELS DO NOT RISE AMONG  
620 TRANSGENDER WOMEN TREATED WITH ESTRADIOL AND SPIRONOLACTONE. *Endocr*  
621 *Pract*. 2018;24(7):646-51.
- 622 38. Millington K, Liu E, Chan YM. The Utility of Potassium Monitoring in Gender-  
623 Diverse Adolescents Taking Spironolactone. *J Endocr Soc*. 2019;3(5):1031-8.
- 624 39. Schagen SE, Cohen-Kettenis PT, Delemarre-van de Waal HA, Hannema SE. Efficacy  
625 and Safety of Gonadotropin-Releasing Hormone Agonist Treatment to Suppress Puberty in Gender  
626 Dysphoric Adolescents. *J Sex Med*. 2016;13(7):1125-32.
- 627 40. Hruz PW. Deficiencies in Scientific Evidence for Medical Management of Gender  
628 Dysphoria. *Linacre Q*. 2020;87(1):34-42.
- 629 41. Schagen SEE, Wouters FM, Cohen-Kettenis PT, Gooren LJ, Hannema SE. Bone  
630 Development in Transgender Adolescents Treated With GnRH Analogues and Subsequent Gender-  
631 Affirming Hormones. *J Clin Endocrinol Metab*. 2020;105(12).
- 632 42. Olson-Kennedy J, Chan YM, Rosenthal S, Hidalgo MA, Chen D, Clark L, Ehrensaft  
633 D, Tishelman A, Garofalo R. Creating the Trans Youth Research Network: A Collaborative  
634 Research Endeavor. *Transgend Health*. 2019;4(1):304-12.
- 635 43. Jensen RK, Jensen JK, Simons LK, Chen D, Rosoklija I, Finlayson CA. Effect of  
636 Concurrent Gonadotropin-Releasing Hormone Agonist Treatment on Dose and Side Effects of  
637 Gender-Affirming Hormone Therapy in Adolescent Transgender Patients. *Transgend Health*.  
638 2019;4(1):300-3.
- 639 44. Khatchadourian K, Amed S, Metzger DL. Clinical management of youth with gender  
640 dysphoria in Vancouver. *J Pediatr*. 2014;164(4):906-11.
- 641 45. Mattawanon N, Spencer JB, Schirmer DA, 3rd, Tangpricha V. Fertility preservation  
642 options in transgender people: A review. *Rev Endocr Metab Disord*. 2018;19(3):231-42.
- 643 46. Irwig MS. Is there a role for 5 $\alpha$ -reductase inhibitors in transgender individuals?  
644 *Andrology*. 2020.
- 645 47. Leinung MC, Feustel PJ, Joseph J. Hormonal Treatment of Transgender Women with  
646 Oral Estradiol. *Transgend Health*. 2018;3(1):74-81.
- 647 48. Lamb CA, Fabris VT, Lanari C. Progesterone and breast. *Best Pract Res Clin Obstet*  
648 *Gynaecol*. 2020.
- 649 49. Wamboldt R, Shuster S, Sidhu BS. Lactation Induction in a Transgender Woman  
650 Wanting to Breastfeed: Case Report. *J Clin Endocrinol Metab*. 2021.
- 651 50. Wierckx K, Gooren L, T'Sjoen G. Clinical review: Breast development in trans  
652 women receiving cross-sex hormones. *J Sex Med*. 2014;11(5):1240-7.

- 653 51. Prior JC. Progesterone Is Important for Transgender Women's Therapy-Applying  
654 Evidence for the Benefits of Progesterone in Ciswomen. *J Clin Endocrinol Metab.*  
655 2019;104(4):1181-6.
- 656 52. Iwamoto SJ, T'Sjoen G, Safer JD, Davidge-Pitts CJ, Wierman ME, Glodowski MB,  
657 Rothman MS. Letter to the Editor: "Progesterone is Important for Transwomen's Therapy-applying  
658 evidence for the benefits of progesterone in ciswomen". *J Clin Endocrinol Metab.* 2019.
- 659 53. Hartley RL, Stone JP, Temple-Oberle C. Breast cancer in transgender patients: A  
660 systematic review. Part 1: Male to female. *Eur J Surg Oncol.* 2018;44(10):1455-62.
- 661 54. Asi N, Mohammed K, Haydour Q, Gionfriddo MR, Vargas OL, Prokop LJ, Faubion  
662 SS, Murad MH. Progesterone vs. synthetic progestins and the risk of breast cancer: a systematic  
663 review and meta-analysis. *Syst Rev.* 2016;5(1):121.
- 664 55. Seligowski AV, Hurly J, Mellen E, Ressler KJ, Ramikie TS. Translational studies of  
665 estradiol and progesterone in fear and PTSD. *Eur J Psychotraumatol.* 2020;11(1):1723857.
- 666 56. Bristot G, Ascoli B, Gubert C, Panizzutti B, Kapczinski F, Rosa AR. Progesterone and  
667 its metabolites as therapeutic targets in psychiatric disorders. *Expert Opin Ther Targets.*  
668 2014;18(6):679-90.
- 669 57. Roomruangwong C, Carvalho AF, Comhaire F, Maes M. Lowered Plasma Steady-  
670 State Levels of Progesterone Combined With Declining Progesterone Levels During the Luteal  
671 Phase Predict Peri-Menstrual Syndrome and Its Major Subdomains. *Front Psychol.* 2019;10:2446.
- 672 58. Skovlund CW, Mørch LS, Kessing LV, Lidegaard Ø. Association of Hormonal  
673 Contraception With Depression. *JAMA Psychiatry.* 2016;73(11):1154-62.
- 674 59. Trifu S, Vladuti A, Popescu A. THE NEUROENDOCRINOLOGICAL ASPECTS OF  
675 PREGNANCY AND POSTPARTUM DEPRESSION. *Acta Endocrinol (Buchar).* 2019;15(3):410-  
676 5.
- 677 60. Skouby SO, Sidelmann JJ. Impact of progestogens on hemostasis. *Horm Mol Biol*  
678 *Clin Investig.* 2018;37(2).
- 679 61. Canonico M. Hormone therapy and hemostasis among postmenopausal women: a  
680 review. *Menopause.* 2014;21(7):753-62.
- 681 62. Quinkler M, Diederich S, Bahr V, Oelkers W. The role of progesterone metabolism  
682 and androgen synthesis in renal blood pressure regulation. *Horm Metab Res.* 2004;36(6):381-6.
- 683 63. Baker ME, Katsu Y. Progesterone: An enigmatic ligand for the mineralocorticoid  
684 receptor. *Biochem Pharmacol.* 2020;177:113976.
- 685 64. Dekker MJ, Wierckx K, Van Caenegem E, Klaver M, Kreukels BP, Elaut E, Fisher  
686 AD, van Trotsenburg MA, Schreiner T, den Heijer M, et al. A European Network for the  
687 Investigation of Gender Incongruence: Endocrine Part. *J Sex Med.* 2016;13(6):994-9.
- 688 65. de Blok CJM, Klaver M, Wiepjes CM, Nota NM, Heijboer AC, Fisher AD, Schreiner  
689 T, T'Sjoen G, den Heijer M. Breast Development in Transwomen After 1 Year of Cross-Sex  
690 Hormone Therapy: Results of a Prospective Multicenter Study. *J Clin Endocrinol Metab.*  
691 2018;103(2):532-8.
- 692 66. de Blok CJM, Dijkman BAM, Wiepjes CM, Staphorsius AS, Timmermans FW, Smit  
693 JM, Dreijerink KMA, den Heijer M. Sustained breast development and breast anthropometric  
694 changes in three years gender-affirming hormone treatment. *J Clin Endocrinol Metab.* 2020.
- 695 67. Seal LJ, Franklin S, Richards C, Shishkareva A, Sinclair C, Barrett J. Predictive  
696 markers for mammoplasty and a comparison of side effect profiles in transwomen taking various  
697 hormonal regimens. *J Clin Endocrinol Metab.* 2012;97(12):4422-8.
- 698 68. Spanos C, Bretherton I, Zajac JD, Cheung AS. Effects of gender-affirming hormone  
699 therapy on insulin resistance and body composition in transgender individuals: A systematic review.  
700 *World J Diabetes.* 2020;11(3):66-77.

- 701 69. Harper J, O'Donnell E, Sorouri Khorashad B, McDermott H, Witcomb GL. How does  
702 hormone transition in transgender women change body composition, muscle strength and  
703 haemoglobin? Systematic review with a focus on the implications for sport participation. *Br J*  
704 *Sports Med.* 2021.
- 705 70. Ristori J, Cocchetti C, Castellini G, Pierdominici M, Cipriani A, Testi D, Gavazzi G,  
706 Mazzoli F, Mosconi M, Meriggiola MC, et al. Hormonal Treatment Effect on Sexual Distress in  
707 Transgender Persons: 2-Year Follow-Up Data. *J Sex Med.* 2020;17(1):142-51.
- 708 71. Giltay EJ, Gooren LJ. Effects of sex steroid deprivation/administration on hair growth  
709 and skin sebum production in transsexual males and females. *J Clin Endocrinol Metab.*  
710 2000;85(8):2913-21.
- 711 72. Bradford NJ, Rider GN, Spencer KG. Hair removal and psychological well-being in  
712 transfeminine adults: associations with gender dysphoria and gender euphoria. *J Dermatolog Treat.*  
713 2019:1-8.
- 714 73. Motmans J, Meier P, Ponnet K, T'Sjoen G. Female and male transgender quality of  
715 life: socioeconomic and medical differences. *J Sex Med.* 2012;9(3):743-50.
- 716 74. Aldridge Z, Patel S, Guo B, Nixon E, Pierre Bouman W, Witcomb GL, Arcelus J.  
717 Long-term effect of gender-affirming hormone treatment on depression and anxiety symptoms in  
718 transgender people: A prospective cohort study. *Andrology.* 2020.
- 719 75. Baker KE, Wilson LM, Sharma R, Dukhanin V, McArthur K, Robinson KA.  
720 Hormone Therapy, Mental Health, and Quality of Life Among Transgender People: A Systematic  
721 Review. *J Endocr Soc.* 2021;5(4):bvab011.
- 722 76. Liu RT, Sheehan AE, Walsh RFL, Sanzari CM, Cheek SM, Hernandez EM.  
723 Prevalence and correlates of non-suicidal self-injury among lesbian, gay, bisexual, and transgender  
724 individuals: A systematic review and meta-analysis. *Clin Psychol Rev.* 2019;74:101783.
- 725 77. Frokjaer VG. Pharmacological sex hormone manipulation as a risk model for  
726 depression. *J Neurosci Res.* 2020;98(7):1283-92.
- 727 78. Edwards AC, Lönn SL, Crump C, Mościcki EK, Sundquist J, Kendler KS, Sundquist  
728 K. Oral contraceptive use and risk of suicidal behavior among young women. *Psychol Med.* 2020:1-  
729 8.
- 730 79. Eriksson E, Sundblad C, Lisjö P, Modigh K, Andersch B. Serum levels of androgens  
731 are higher in women with premenstrual irritability and dysphoria than in controls.  
732 *Psychoneuroendocrinology.* 1992;17(2-3):195-204.
- 733 80. Kristensen TT, Christensen LL, Frystyk J, Glintborg D, T'Sjoen G, Roessler KK,  
734 Andersen MS. Effects of testosterone therapy on constructs related to aggression in transgender  
735 men: A systematic review. *Horm Behav.* 2020:104912.
- 736 81. Defreyne J, T'Sjoen G, Bouman WP, Brewin N, Arcelus J. Prospective Evaluation of  
737 Self-Reported Aggression in Transgender Persons. *J Sex Med.* 2018;15(5):768-76.
- 738 82. Wierckx K, Elaut E, Van Hoorde B, Heylens G, De Cuypere G, Monstrey S, Weyers  
739 S, Hoebeke P, T'Sjoen G. Sexual desire in trans persons: associations with sex reassignment  
740 treatment. *J Sex Med.* 2014;11(1):107-18.
- 741 83. Kerckhof ME, Kreukels BPC, Nieder TO, Becker-Héblly I, van de Grift TC,  
742 Staphorsius AS, Köhler A, Heylens G, Elaut E. Prevalence of Sexual Dysfunctions in Transgender  
743 Persons: Results from the ENIGI Follow-Up Study. *J Sex Med.* 2019;16(12):2018-29.
- 744 84. Connelly PJ, Marie Freel E, Perry C, Ewan J, Touyz RM, Currie G, Delles C. Gender-  
745 Affirming Hormone Therapy, Vascular Health and Cardiovascular Disease in Transgender Adults.  
746 *Hypertension.* 2019;74(6):1266-74.

- 747 85. Maraka S, Singh ON, Rodriguez-Gutierrez R, Davidge-Pitts CJ, Nippoldt TB, Prokop  
748 LJ, Murad MH. Sex Steroids and Cardiovascular Outcomes in Transgender Individuals: A  
749 Systematic Review and Meta-Analysis. *J Clin Endocrinol Metab.* 2017;102(11):3914-23.
- 750 86. El Khoudary SR, Aggarwal B, Beckie TM, Hodis HN, Johnson AE, Langer RD,  
751 Limacher MC, Manson JE, Stefanick ML, Allison MA. Menopause Transition and Cardiovascular  
752 Disease Risk: Implications for Timing of Early Prevention: A Scientific Statement From the  
753 American Heart Association. *Circulation.* 2020;142(25):e506-e32.
- 754 87. Aryan L, Younessi D, Zargari M, Banerjee S, Agopian J, Rahman S, Borna R,  
755 Ruffenach G, Umar S, Eghbali M. The Role of Estrogen Receptors in Cardiovascular Disease. *Int J*  
756 *Mol Sci.* 2020;21(12).
- 757 88. Getahun D, Nash R, Flanders WD, Baird TC, Becerra-Culqui TA, Cromwell L,  
758 Hunkeler E, Lash TL, Millman A, Quinn VP, et al. Cross-sex Hormones and Acute Cardiovascular  
759 Events in Transgender Persons: A Cohort Study. *Ann Intern Med.* 2018;169(4):205-13.
- 760 89. Scheres LJJ, Selier NLD, Nota NM, van Diemen JJK, Cannegieter SC, den Heijer M.  
761 Effect of gender-affirming hormone use on coagulation profiles in transmen and transwomen. *J*  
762 *Thromb Haemost.* 2021;19(4):1029-37.
- 763 90. Shatzel JJ, Connelly KJ, DeLoughery TG. Thrombotic issues in transgender medicine:  
764 A review. *Am J Hematol.* 2017;92(2):204-8.
- 765 91. Scarabin PY. Progestogens and venous thromboembolism in menopausal women: an  
766 updated oral versus transdermal estrogen meta-analysis. *Climacteric.* 2018;21(4):341-5.
- 767 92. Kuhl H. Pharmacology of estrogens and progestogens: influence of different routes of  
768 administration. *Climacteric.* 2005;8 Suppl 1:3-63.
- 769 93. Wiepjes CM, de Jongh RT, de Blok CJ, Vlot MC, Lips P, Twisk JW, den Heijer M.  
770 Bone Safety During the First Ten Years of Gender-Affirming Hormonal Treatment in Transwomen  
771 and Transmen. *J Bone Miner Res.* 2019;34(3):447-54.
- 772 94. Singh-Ospina N, Maraka S, Rodriguez-Gutierrez R, Davidge-Pitts C, Nippoldt TB,  
773 Prokop LJ, Murad MH. Effect of Sex Steroids on the Bone Health of Transgender Individuals: A  
774 Systematic Review and Meta-Analysis. *J Clin Endocrinol Metab.* 2017;102(11):3904-13.
- 775 95. Vlot MC, Wiepjes CM, de Jongh RT, T'Sjoen G, Heijboer AC, den Heijer M. Gender-  
776 Affirming Hormone Treatment Decreases Bone Turnover in Transwomen and Older Transmen. *J*  
777 *Bone Miner Res.* 2019;34(10):1862-72.
- 778 96. Wiepjes CM, de Blok CJ, Staphorsius AS, Nota NM, Vlot MC, de Jongh RT, den  
779 Heijer M. Fracture Risk in Trans Women and Trans Men Using Long-Term Gender-Affirming  
780 Hormonal Treatment: A Nationwide Cohort Study. *J Bone Miner Res.* 2020;35(1):64-70.
- 781 97. Motta G, Marinelli L, Barale M, Brustio PR, Manieri C, Ghigo E, Procopio M,  
782 Lanfranco F. Fracture risk assessment in an Italian group of transgender women after gender-  
783 confirming surgery. *J Bone Miner Metab.* 2020;38(6):885-93.
- 784 98. Jackson SS, Han X, Mao Z, Nogueira L, Suneja G, Jemal A, Shiels MS. Cancer Stage,  
785 Treatment, and Survival among Transgender Patients in the United States. *J Natl Cancer Inst.* 2021.
- 786 99. Maglione KD, Margolies L, Jaffer S, Szabo J, Schmidt H, Weltz C, Sonnenblick EB.  
787 Breast cancer in male-to-female transsexuals: use of breast imaging for detection. *AJR Am J*  
788 *Roentgenol.* 2014;203(6):W735-40.
- 789 100. de Nie I, de Blok CJM, van der Sluis TM, Barbé E, Pigot GLS, Wiepjes CM, Nota  
790 NM, van Mello NM, Valkenburg NE, Huirne J, et al. Prostate Cancer Incidence under Androgen  
791 Deprivation: Nationwide Cohort Study in Trans Women Receiving Hormone Treatment. *J Clin*  
792 *Endocrinol Metab.* 2020;105(9):e3293-9.

793 101. Sharif A, Malhotra NR, Acosta AM, Kajdacsy-Balla AA, Bosland M, Guzman G,  
794 Prins GS, Abern MR. The Development of Prostate Adenocarcinoma in a Transgender Male to  
795 Female Patient: Could Estrogen Therapy Have Played a Role? *Prostate*. 2017;77(8):824-8.  
796 102. Barzi A, Lenz AM, Labonte MJ, Lenz HJ. Molecular pathways: Estrogen pathway in  
797 colorectal cancer. *Clin Cancer Res*. 2013;19(21):5842-8.  
798 103. Xie SH, Lagergren J. The Male Predominance in Esophageal Adenocarcinoma. *Clin*  
799 *Gastroenterol Hepatol*. 2016;14(3):338-47.e1.  
800 104. Xie SH, Ness-Jensen E, Rabbani S, Langseth H, Gislefoss RE, Mattsson F, Lagergren  
801 J. Circulating Sex Hormone Levels and Risk of Esophageal Adenocarcinoma in a Prospective Study  
802 in Men. *Am J Gastroenterol*. 2020;115(2):216-23.  
803 105. Middle JG, Kane JW. Oestradiol assays: fitness for purpose? *Ann Clin Biochem*.  
804 2009;46(Pt 6):441-56.  
805 106. Fernández R, Delgado-Zayas E, Ramírez K, Cortés-Cortés J, Gómez-Gil E, Esteva I,  
806 Almaraz MC, Guillamon A, Pásaro E. Analysis of Four Polymorphisms Located at the Promoter of  
807 the Estrogen Receptor Alpha ESR1 Gene in a Population With Gender Incongruence. *Sex Med*.  
808 2020;8(3):490-500.  
809 107. Darabi M, Ani M, Panjehpour M, Rabbani M, Movahedian A, Zarean E. Effect of  
810 estrogen receptor  $\beta$  A1730G polymorphism on ABCA1 gene expression response to  
811 postmenopausal hormone replacement therapy. *Genet Test Mol Biomarkers*. 2011;15(1-2):11-5.  
812 108. Jellinger PS, Handelsman Y, Rosenblit PD, Bloomgarden ZT, Fonseca VA, Garber  
813 AJ, Grunberger G, Guerin CK, Bell DSH, Mechanick JI, et al. AMERICAN ASSOCIATION OF  
814 CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY  
815 GUIDELINES FOR MANAGEMENT OF DYSLIPIDEMIA AND PREVENTION OF  
816 CARDIOVASCULAR DISEASE. *Endocr Pract*. 2017;23(Suppl 2):1-87.  
817 109. Periti P, Mazzei T, Mini E. Clinical pharmacokinetics of depot leuprorelin. *Clin*  
818 *Pharmacokinet*. 2002;41(7):485-504.  
819  
820  
821

822 Figure legend:

823

824 **Figure 1:**

825

826 Feminizing treatment. Balance between desired effects and potential side effects and a list of most important

827 risk factors (modifiable and non-modifiable).

**Table 1: GAHT, recommended treatment modalities in transgender women.**

Content	Administration form	Content	Dosage	Time to peak	Farmacokinetics
E2	Patch	E2 in polymeric acrylate or vinylacetate	One patch every 3 days 0.05-0.15 mg E2/24h	8-12 hours	E1/E2 ratio 1 Constant delivery of E2 during 7 days No accumulation of E2 Half-life 24 hours
	Gel/spray	E2 in alcoholic gel	Gel daily 0.8 – 3 mg/day	4-6 hours	E1/E2 ratio 1 No accumulation of E2 Steady state within 3 days Half-life 36 hours
	Tablet	E2	2-6 mg/day	2-4 hours	High E1/E2 ratio (due to first pass metabolism in gut and liver) Gradual accumulation of E2 in blood Steady state reached within days Half-life 12 hours
	Intramuscular injection	E2 in oily solution	2-10 mg/injection every 1-2 weeks (depending on solution)	2-4 days (depending on solution)	E1/E2 ratio 0.5 Half-life 1-2 weeks
Cyproterone acetate	Tablet	Cyproterone acetate	≤10 mg/day	2-3 hours	Metabolized in liver Half-life 48-72 hours
Spironolactone	Tablet	Spironolactone	100-400 mg/day	1-4 hours	Metabolized in liver Half-life 16-22 hours
GnRH-a	Subcutaneous or intramuscular injection	Leuprolide/ Triptoreline	3.75 - 45 mg/ 1-6 months	1-4 hours	Metabolized in liver Half-life 3 hours

Information adapted from (3, 92, 109)

E1: Estrone, E2: Estradiol

Note: Not currently recommended GAHT modalities are not included in the table (5-alfa reductase inhibitors, flutamide, progesterone etc).

**Table 2. GAHT, directions for choice of treatment**

	1 <sup>st</sup> choice	2 <sup>nd</sup> choice	Not recommended	Debated
Estrogen	E2 <ul style="list-style-type: none"> <li>• Dermal</li> <li>• Oral (&lt; 40 years old)</li> </ul>	E2 <ul style="list-style-type: none"> <li>• Oral</li> </ul>	Oral contraceptives	Buccal E2
Anti-androgen	Spirolactone CPA GnRH-a		5-alfa reductase inhibitors Flutamide	CPA vs. spironolactone vs. GnRH-a  Timing of orchiectomy  Reduction of CPA dosage
Adjunctive treatment				Progesterone <ul style="list-style-type: none"> <li>• Natural vs. progestins</li> </ul>

E2: Estradiol

CPA: Cyproterone acetate



## Desired effects

### Feminizing effects

- Breast
- Waist/hip ratio
- Facial and body hair

### Mental status

- Quality of life
- Mental health

**Gender affirming  
hormonal treatment  
GAHT**

### Risk factors

#### Modifiable

- GAHT
- BMI
- Physical activity
- Smoking
- Blood pressure
- Lipid status
- Glucose status

#### Non-modifiable

- Age
- Natal gender
- Morbidity

## Potential side effects

### Infertility

### Cardiovascular disease

- Arterial
- Venous

### Bone fracture

### Cancer

- Breast cancer risk
- Change in other cancer risk