Medroxyprogesterone Acetate in Gender-Affirming Therapy for Transwomen: Results From a Retrospective Study

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Context: Medroxyprogesterone acetate (MPA) is a widely used progestin in feminizing hormone therapy. However, the side effects and hormonal changes elicited by this drug have never been investigated in the transgender population.

Objective: We evaluated the incidence of self-reported effects among transwomen using MPA and this drug's impact on hormonal and metabolic parameters.

Design, Setting, and Participants: We retrospectively collected data from 290 follow-up visits (FUVs) of transwomen treated at Rhode Island Hospital from January 2011 to July 2018 (mean duration of therapy 3.4 ± 1.7 years). FUVs followed regimens of estradiol (E) and spironolactone, with MPA (n = 102) or without MPA (n = 188).

Main Outcome Measures: We assessed the incidence of self-reported effects after MPA treatment. We also compared blood levels of E, testosterone, and various laboratory parameters between MPA and non-MPA groups.

Results: Mean weighted E level was 211 ± 57 pg/mL after MPA treatment and 210 ± 31 pg/mL otherwise; this difference was nonsignificant [$t(274) = 0.143$, $P = 0.886$]. Mean weighted testosterone level was 79 ± 18 ng/dL after MPA treatment and 215 ± 29 ng/dL otherwise; testosterone levels were significantly lower in the MPA group [$t(122) = 32.4$, $P < 0.001$]. There were minimal changes in other laboratory parameters. Of 39 patients receiving MPA, 26 reported improved breast development and 11 reported decreased facial hair. Five patients experienced mood swings on MPA.

Conclusions: In our cohort of transwomen, we found minimal side effects, unchanged E levels, and a decline in testosterone associated with MPA, outcomes consistent with feminization. Prospective studies are needed to confirm our findings. (***J Clin Endocrinol Metab*** **104: 5148–5156, 2019)**

1-3
3 notes:

Gender dysphoria (GD) is a state of distress caused by discord between a person's gender identity and their assigned sex (1). Gender-affirming hormone (GAH) therapy aims to alleviate GD by replacing endogenous hormones with those of the asserted gender (2). The physical transformation brought on by GAH therapy is associated with improved mental health outcomes in patients with GD (3).

A large proportion of patients with GD are transwomen: natal males identifying as female (4). The goal of GAH therapy in this subset of patients with GD is to increase serum levels of estradiol (E) and promote its

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Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; BUN, blood urea nitrogen; E, estradiol; FUV, follow-up visit; GAH, gender-affirming hormone; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone agonist; Hct, hematocrit; HPG, hypothalamic-pituitary-gonadal; MPA, medroxyprogesterone acetate; VTE, venous thromboembolism.

feminizing effects and to decrease levels of testosterone and suppress its masculinizing effects. Therefore, a typical regimen for the adult transwoman consists of bioidentical 17-β E and an antiandrogen such as spironolactone (5). Natural progesterone and synthetic progestins are often added to further suppress androgens and increase feminization (2, 5, 6).

Medroxyprogesterone acetate (MPA) is a common progestin used in feminizing GAH therapy (5, 6). Despite its widespread use among transwomen, MPA has not yet been investigated in the context of transgender care (5, 6). Although many studies have evaluated MPA as a mode of contraception or in postmenopausal hormone therapy, the relevance of these studies to transgender people is questionable. Rather than measuring parameters relevant to feminization, previous work has focused on long-term side effects, contraceptive efficacy, and alleviation of menopausal symptoms (7–10). Additionally, observations from natal females may not translate to natal males. Although studies of MPA have been conducted in men (*e.g.*, those with paraphilia or prostate cancer), they use large dosages and adjunctive medications that are uncommon in transgender care (11, 12).

Therefore, the aim of this study was to retrospectively analyze clinical outcomes with and without MPA in a cohort of transwomen. In particular, we assessed the incidence of side effects and desired effects after initiation of MPA, as well as levels of serum E, serum testosterone, and various laboratory parameters.

Materials and Methods

These research methods were approved by the Rhode Island Hospital review board (Providence, RI). All patients in this study received care at our Gender and Sexual Health Services clinic and provided written informed consent. Transfeminine gender identity was assessed by current clinical standards. (Note that we herein refer to "transfeminine patients" as "transwomen" for brevity, but this group includes all feminine gender identities.) Diagnoses of GD were based on criteria outlined in the *Diagnostic and Statistical Manual of Mental Disorders*–Fifth Edition and by current clinical standards (13).

In our clinic, GAH therapy is initiated after extensive psychosocial assessment, review of patient medical history, and gender interview with patient or parents. The initial regimen for asserted females typically consists of sublingual E (2, 4, or 6 mg) and an antiandrogen (*e.g.*, spironolactone, finasteride). Given the known thrombogenic effects of sublingual E, this medication is contraindicated in heavy smokers, patients with diabetes, and patients with deep vein thrombosis or other cardiovascular risk factors. (Some of these high-risk patients may receive transdermal instead of sublingual E.) Patient follow-up visits (FUVs) generally occur 3 months apart for the first year of treatment and annually thereafter. Levels of serum E and various biochemical parameters may be obtained at each FUV. These data inform adjustments to the initial dosage of E to achieve goal concentration of 100 to 350 pg/mL serum E. E dosage is usually reduced if the serum E level is persistently elevated above 350 pg/mL. Later in the course of therapy, progestins (*e.g.*, MPA) may be prescribed to further suppress testosterone levels and promote breast development. The addition of a progestin is generally a matter of patient preference, provided that there are no clinical contraindications.

In this study, data from each FUV were grouped by the regimen followed by the patient for the preceding 3+ months. Therefore, data collected after regimens with and without MPA were in separate groups for analysis. Data obtained after regimens with different dosages of E were also grouped separately, enabling comparison of MPA and non-MPA groups at each E dosage level. We included only FUVs from patients following regimens of sublingual E (2 to 12 mg daily) and spironolactone (100 to 200 mg daily), with or without MPA [5 to 10 mg daily (sublingual tablet) or 150 mg every 3 months (intramuscular injection)].

Data Inclusion

Our final dataset consisted of 290 FUVs from a total of 92 patients seen in our clinic from January 2011 to July 2018 (14). These FUVs were identified by application of a series of exclusion criteria to a raw dataset of 632 FUVs. We excluded 177 FUVs because patients followed a GAH regimen without medications of interest to this study (E, spironolactone). Another 57 FUVs were excluded because of the presence of other medications (most commonly finasteride, leuprolide, or prometrium). Another 66 FUVs were excluded because data were collected after orchidectomy. Finally, 42 FUVs were excluded because of lack of adherence to the regimen (*i.e.*, missing doses frequently, self-adjusting dosage, self-prescribing medications).

In our final dataset, there were no more than six FUVs from any one patient. Of the 290 FUVs, 102 (from 47 patients collectively) were associated with regimens containing MPA. The number of FUVs in each regimen category (grouped by E dosage and presence of MPA) is displayed in Table 1. Mean age of patients was 31.0 ± 7.1 years (range 14 to 69 years), and mean length of therapy was 3.4 ± 1.7 years.

Outcome Measures

We recorded any adverse events, side effects, or desired effects reported by patient or noted by provider during GAH therapy.

Values for hormonal and biochemical parameters were recorded during (most) FUVs. In particular, we analyzed levels of total testosterone, 17-β E, prolactin, hemoglobin, hematocrit, glucose, blood urea nitrogen (BUN), creatinine, sodium, potassium, chloride, calcium, albumin, bilirubin, alkaline

Table 1. Number of FUVs Analyzed in Each Regimen Group

	With MPA	Without MPA
2 mg E	n/a	n = 15
4 mg E	n = 14	n = 29
6 mg E	n = 16	n = 61
8 mg E	n = 40	n = 49
10 mg E	n = 25	n = 28
12 mg E	n = 7	n = 6
All dosages	n = 102	n = 188

Baseline: n = 92.

Abbreviation: n/a, not available.

phosphatase (ALP), total protein, aspartate transaminase (AST), and alanine transaminase (ALT). All parameters except for testosterone and E were also measured at baseline (*i.e.,* before initiation of GAH therapy). E and testosterone were assayed by high-pressure liquid chromatography/tandem mass spectrometry (Esoterix, Englewood, CO). Reference ranges for serum E were 5.0 to 36.0 pg/mL in prepubescent girls, 30 to 100 pg/mL in the follicular stage, 70 to 300 pg/mL in the luteal stage, <15 pg/mL in postmenopausal women, and 8.0 to 35 pg/mL in natal males. Reference ranges for serum testosterone were 10 to 55 in ng/dL in premenopausal women, 7 to 40 ng/dL in postmenopausal women, and 348 to 1197 ng/dL in natal adult males. Reference ranges for other laboratory parameters were as follows: 2 to 17 ng/mL for prolactin, 13.5 to 16.0 g/dL for hemoglobin, 37.0% to 47.0% for hematocrit, 67 to 99 mg/dL for glucose, 6 to 24 mg/dL for BUN, 0.64 to 1.27 mg/dL for creatinine, 135 to 145 mEq/L for sodium, 3.6 to 5.1 mEq/L for potassium, 98 to 110 mEq/L for chloride, 8.5 to 10.5 mEq/dL for calcium, 3.5 to 5.0 g/dL for albumin, 0.2 to 1.3 mg/dL for bilirubin, 34 to 104 IU/L for ALP, 6.0 to 8.0 g/dL for total protein, 6 to 45 IU/L for AST, and 10 to 42 IU/L for ALT.

Statistics

Statistical tests were aimed at evaluating differences in hormonal and biochemical parameters between regimen groups (*e.g.,* regimens with and without MPA). In our clinic, MPA is more likely to be prescribed later in the course of GAH therapy and is therefore correlated with higher E dosages. To limit this difference from confounding our analysis, we compared MPA and non-MPA groups at the level of each E dosage.

Serum E levels in MPA and non-MPA groups were modeled by weighted linear regression as a function of E dosage. Regression was robust against nonnormality of residuals given the large sample size (15). Homoscedasticity was assessed by Breusch-Pagan test. After the assumptions of regression were met, differences in slope and least-squares mean were evaluated by Student *t* tests. Serum testosterone levels were analyzed similarly but were regressed against serum E levels rather than E dosage because of limited data availability.

For other laboratory parameters, normality of residuals in each regimen group was assessed by Kolmogorov-Smirnov test. Equality of variance was assessed by Levene test. In the case of equal variance between groups, one-way ANOVA was performed, followed by Student *t* test *post hoc*. In the case of unequal variance, Welch ANOVA was performed, followed by Games-Howell test *post hoc*. For each laboratory parameter, *post hoc* tests evaluated differences in mean values between MPA and non-MPA groups and between groups and baseline. Bonferroni correction was applied to adjust for multiple comparisons.

All *t* tests were one-tailed for directional hypotheses and two-tailed otherwise. All continuous data were reported as mean ± SD.

Analysis was conducted in MatLab R2018a (MathWorks, Inc, Natick, MA). $P < 0.05$ was considered significant.

Results

Data were taken from 290 FUVs with 92 transwomen. Of 39 patients receiving MPA, 26 (67%) reported improved breast development, and 11 (28%) reported decreased facial hair after MPA treatment. The most common side effect of MPA was occurrence of mood swings (13%). One patient elected to discontinue MPA for this reason, after which mood swings resolved. Over the 7-year period in which data were collected, there were no incidents of venous thromboembolism (VTE), cardiovascular disease, prolactinoma, galactorrhea, cholelithiasis, breast cancer, or type II diabetes after initiation of MPA. There were no occurrences of hypotension or hyperkalemia that were clinically significant (*i.e.,* necessitating intervention or adjusted regimen).

A total of 96% of FUVs reported a serum 17-β E level. The remaining 4% of FUVs did not report these data because of patient refusal of laboratories or issues with blood sample. Weighted linear regression was used to model E levels as a function of E dosage in the MPA group (n = 98) and non-MPA group (n = 180) (Fig. 1). After weighted transformation of residuals, data were not significantly heteroscedastic ($P = 0.186$, Breusch-Pagan test). Our weighted model explained 27.8% of variance in MPA data and 29.1% of variance in non-MPA data. Slope of the estimate was 35.9 ± 7.6 for MPA data and 34.3 ± 4.8 for non-MPA data, both of which were greater than zero [$t(96) = 47.1$, $P < 0.001$ and $t(178) = 95.8$, $P < 0.001$, respectively]. Slopes were not significantly different [$t(274) = 1.93$, $P = 0.055$]. Weighted least-squares mean was 211 ± 57 pg/mL for MPA data and 210 ± 31 pg/mL for non-MPA data; the difference in mean E level was nonsignificant [$t(274) = 0.143$, $P = 0.886$].

A total of 47% of FUVs documented a total serum testosterone level. Because multiple regimen groups were entirely lacking in testosterone data, we regressed testosterone level against E level rather than E dosage (Fig. 2). Weighted data were not significantly heteroscedastic ($P = 0.94$, Breusch-Pagan test). Our weighted model explained 20.0% of variance in MPA data (n = 47) and 14.8% of variance in non-MPA data (n = 90). Slope was −0.15 ± 0.07 for the MPA estimate and −0.32 ± 0.12 for the non-MPA estimate, both of which were <0 [$t(43) = 13.3$, $P < 0.001$ and $t(79) = 23.6$, $P < 0.001$, respectively]. Slope of MPA estimate was significantly greater than slope of non-MPA estimate [$t(122) = 10.1$, $P < 0.001$]. Weighted least-squares mean was 79 ± 18 ng/dL for MPA data and 215 ± 29 ng/dL for non-MPA data. Mean testosterone level of the MPA group was significantly lower than that of the non-MPA group [$t(122) = 32.4$, $P < 0.001$].

In any regimen group, 0% to 51% of FUVs were missing data for biochemical parameters. At an E dosage of 12 mg, data were insufficient (n < 5) for most parameters, so this group was excluded from analysis. All laboratory data were normally distributed ($P < 0.05$,

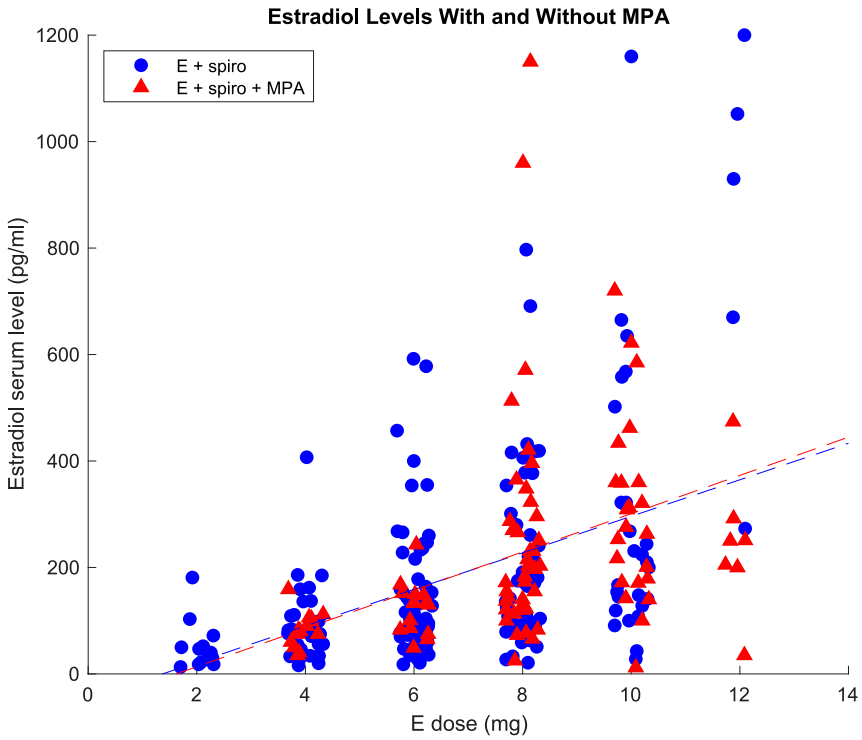

Figure 1. Serum E vs dosage of E in patients adhering to regimens of E and spironolactone (spiro), with or without MPA.

Kolgomorov-Smirnov test). Threshold for significance was adjusted to $P < 0.0039$ to reduce type I error from multiple comparisons. Classic and Welch ANOVAs revealed no significant variation in levels of glucose, BUN, creatinine, sodium, potassium, chloride, calcium, total protein, ALT, or AST between MPA and non-MPA groups or between groups and baseline (Table 2). Compared with baseline, there was a significant increase in prolactin on E dosages of 6 mg, with and without MPA [Fig. 3(a)]. The difference in prolactin between MPA and non-MPA groups was nonsignificant. Furthermore, hemoglobin and hematocrit were significantly depressed from baseline in all regimen groups [Fig. 3(b) and 3(c)]. At an E dosage of 4 mg, hemoglobin and hematocrit levels were lower with MPA (n = 9) than without MPA (n = 14). Lastly, there was a significant decrease in serum albumin and bilirubin at E dosages ≥6 mg and in ALP at E dosages ≥8 mg [Fig. 3(d)–3(f)]. Differences in albumin, bilirubin, and ALP between MPA and non-MPA groups were nonsignificant.

All mentions of significance imply statistical but not necessarily clinical significance.

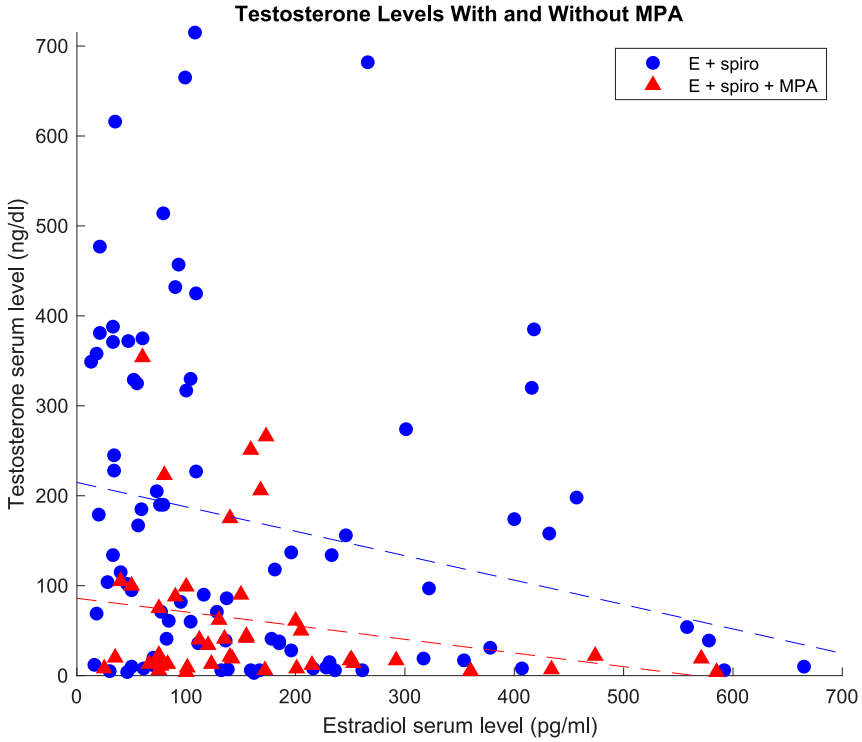

Figure 2. Total serum testosterone vs serum E in patients adhering to regimens of E and spironolactone (spiro), with or without MPA.

Discussion

Off-label use of MPA as a feminizing agent in transgender care is widespread but has never been systematically studied. This retrospective study evaluated the use of MPA in a cohort of transwomen. In brief, we found minimal side effects over a period of 3.4 ± 1.7 years, decreased serum testosterone, and unchanged serum E in MPA-treated patients at follow-up. We also found mildly decreased hemoglobin and hematocrit in some MPA-treated patients.

A majority of patients reported increased breast development after MPA treatment, with some reporting decreased facial hair. No serious adverse events were found, although some patients experienced mood swings after receiving MPA, a side effect that has been previously documented (16). We could not distinguish the effects of MPA from those of E and spironolactone, so the specific contribution of MPA to mood swings (and other reported effects) is unclear. Furthermore, because the occurrence

Table 2. Measures of Hormonal and Biochemical Parameters in Each Regimen Group

	Baseline	Group	2 mg E	4 mg E	6 mg E	8 mg E	10 mg E
Prolactin, ng/mL	8.7 ± 4.2	Without MPA	12.2 ± 6.7	9.8 ± 2.9	12.2 ± 3.5[a]	10.7 ± 5.5	10.6 ± 4.6
Reference range 2–17 ng/mL		With MPA	—	12.4 ± 5.3	14.7 ± 5.8[a]	11.8 ± 4.7	11.3 ± 5.6
Hemoglobin, g/dL	15.4 ± 0.8	Without MPA	13.9 ± 0.7[a]	14.5 ± 0.9[a]	14.4 ± 0.7[a]	14.2 ± 0.7[a]	14.1 ± 0.7[a]
Reference range 13.5–16.0 g/dL		With MPA	—	13.4 ± 0.7[a,b]	14.0 ± 0.5[a]	13.6 ± 1.4[a]	13.9 ± 0.7[a]
Hematocrit, %	45.9 ± 2.0	Without MPA	42.9 ± 2.1[a]	42.8 ± 2.5[a]	42.9 ± 2.1[a]	42.3 ± 1.9[a]	41.4 ± 2.6[a]
Reference range 37.0%–47.0%		With MPA	—	37.9 ± 3.4[a,b]	42.0 ± 2.1[a]	41.4 ± 4.5[a]	41.2 ± 1.7[a]
Albumin, g/dL	4.8 ± 0.4	Without MPA	4.5 ± 0.4	4.7 ± 0.3	4.5 ± 0.3[a]	4.5 ± 0.3[a]	4.4 ± 0.4[a]
Reference range 3.5–5.0 g/dL		With MPA	—	4.5 ± 0.3	4.3 ± 0.2[a]	4.4 ± 0.4[a]	4.4 ± 0.2[a]
Bilirubin, mg/dL	0.66 ± 0.25	Without MPA	0.51 ± 0.28	0.56 ± 0.26	0.52 ± 0.17[a]	0.45 ± 0.19[a]	0.45 ± 0.19[a]
Reference range 0.2–1.3 mg/dL		With MPA	—	0.48 ± 0.32	0.43 ± 0.10[a]	0.45 ± 0.20[a]	0.48 ± 0.13[a]
Alkaline phosphatase, IU/L	77.3 ± 25.6	Without MPA	65.1 ± 9.2	62.2 ± 14.5	67.8 ± 25.5	60.4 ± 21.4[a]	52.8 ± 12.8[a]
Reference range 34–104 IU/L		With MPA	—	60.0 ± 23.2	57.7 ± 25.6	50.5 ± 14.4[a]	45.7 ± 9.8[a]
Glucose, mg/dL	92.0 ± 9.6	Without MPA	94.3 ± 6.0	94.2 ± 10.1	92.9 ± 18.8	93.4 ± 11.1	95.6 ± 11.8
Reference range 67–99 mg/dL		With MPA	—	92.2 ± 7.4	93.7 ± 14.6	91.3 ± 12.5	93.2 ± 12.4
BUN, mg/dL	13.2 ± 4.2	Without MPA	13.3 ± 2.7	12.3 ± 3.1	14.7 ± 3.8	12.8 ± 3.6	13.1 ± 3.0
Reference range 6–24 mg/dL		With MPA	—	13.0 ± 4.0	15.4 ± 3.3	14.1 ± 3.7	11.8 ± 3.2
Creatinine, mg/dL	0.88 ± 0.14	Without MPA	0.82 ± 0.13	0.86 ± 0.13	0.86 ± 0.23	0.79 ± 0.14	0.79 ± 0.15
Reference range 0.64–1.27 mg/dL		With MPA	—	0.90 ± 0.10	0.99 ± 0.14	0.78 ± 0.16	0.79 ± 0.17
Sodium, mEq/L	136.0 ± 1.9	Without MPA	136.0 ± 2.4	135.0 ± 2.1	135.0 ± 1.9	136.0 ± 2.3	136.0 ± 1.6
Reference range 135–145 mEq/L		With MPA	—	134.0 ± 2.5	134.0 ± 2.9	135.0 ± 2.5	135.0 ± 2.1
Potassium, mEq/L	4.1 ± 0.3	Without MPA	4.2 ± 0.3	4.2 ± 0.3	4.2 ± 0.4	4.2 ± 0.3	4.0 ± 0.3
Reference range 3.6–5.1 mEq/L		With MPA	—	4.0 ± 0.2	4.3 ± 0.3	4.1 ± 0.3	4.0 ± 0.3
Chloride, mEq/L	103.0 ± 2.1	Without MPA	103.0 ± 2.2	102.0 ± 1.5	102.0 ± 2.1	103.0 ± 2.3	103.0 ± 1.8
Reference range 98–110 mEq/L		With MPA	—	104.0 ± 1.7	103.0 ± 1.0	103.0 ± 2.6	103.0 ± 2.1
Calcium, mg/dL	9.7 ± 0.3	Without MPA	9.7 ± 0.4	9.7 ± 0.3	9.7 ± 0.4	9.7 ± 0.3	9.6 ± 0.4
Reference range 8.5–10.5 mg/dL		With MPA	—	9.5 ± 0.4	9.5 ± 0.3	9.6 ± 0.3	9.6 ± 0.3
Total protein, g/dL	7.5 ± 0.4	Without MPA	7.1 ± 0.4	7.5 ± 0.3	7.6 ± 0.5	7.5 ± 0.6	7.5 ± 0.5
Reference range 6.0–8.0 g/dL		With MPA	—	7.4 ± 0.5	7.4 ± 0.3	7.4 ± 0.6	7.4 ± 0.4
AST, IU/L	20.9 ± 14.6	Without MPA	14.7 ± 6.0	17.9 ± 8.8	21.4 ± 15.2	15.7 ± 9.0	22.4 ± 18.3
Reference range 6–45 IU/L		With MPA	—	14.0 ± 6.8	17.8 ± 4.9	17.0 ± 12.2	16.9 ± 11.5
ALT, IU/L	21.0 ± 7.6	Without MPA	15.0 ± 1.9	17.7 ± 4.4	19.0 ± 5.7	16.8 ± 4.6	19.3 ± 7.3
Reference range 10–42 IU/L		With MPA	—	16.7 ± 5.2	19.3 ± 7.3	17.8 ± 5.0	17.9 ± 6.9

[a]Significance versus baseline.

[b]Significance between groups.

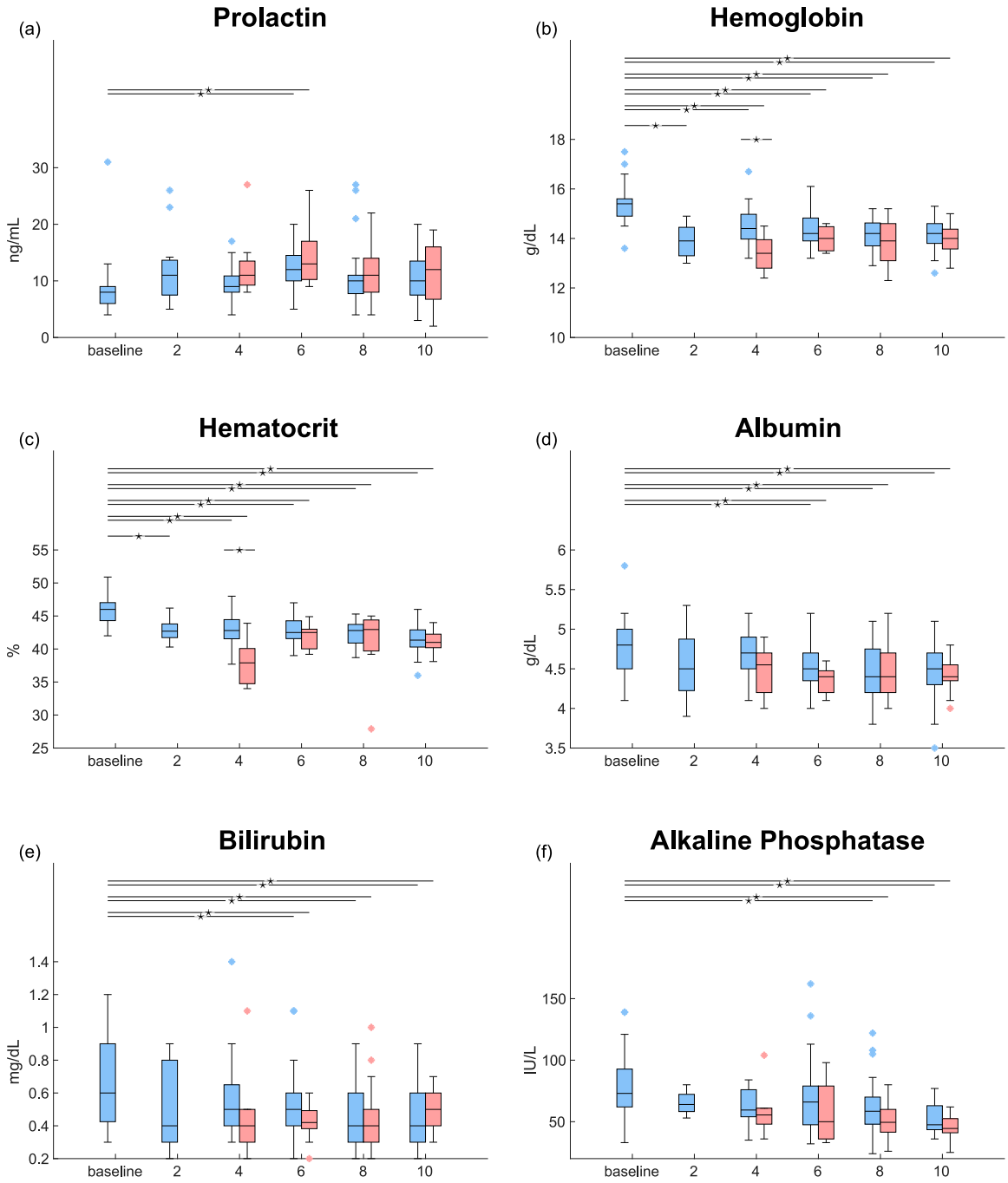

Figure 3. Measures of various biochemical and hormonal parameters at baseline (no treatment) and at varying dosages of E in both MPA and non-MPA groups. Subplots show levels of (a) prolactin, (b) hemoglobin, (c) hematocrit, (d) albumin, (e) bilirubin, and (f) alkaline phosphatase.

of particular side effects was not actively queried, their incidence may have been underestimated. Minor effects such as mild galactorrhea, dermatological changes, and changes in appetite may have gone unnoticed or unreported. Thus, prospective studies should confirm and expand on the results we present here. Furthermore, although we found no clinically significant instances of electrolyte imbalance or hypotension, we recommend monitoring for these conditions given spironolactone's diuretic effects, especially when other sources of abnormality are present.

Levels of total serum testosterone were significantly depressed in MPA-treated transwomen. It is well known that MPA inhibits the hypothalamic-pituitary-gonadal (HPG) axis in women, hence its use as a female contraceptive (17–19). In particular, studies have found lower LH levels after MPA treatment in cisgender women (17–19). In our cohort of transwomen, therefore, the observed decline in testosterone may be attributable to LH suppression. Although some *in vitro* studies suggest that MPA is involved in destabilization of the androgen receptor (20, 21) (which would increase rather than decrease testosterone

levels), we speculate that this effect was minimal in comparison with MPA's inhibition of the HPG axis. Our findings are consistent with previous studies reporting lower plasma testosterone after MPA use in women with hirsutism (22), women seeking contraception (23), and men with paraphilia (12), although dosages given in the latter group were much greater than those used in transgender care. The reduction of testosterone by MPA may contribute to its adjunctive role in feminization.

Levels of serum E in MPA and non-MPA groups were not significantly different. Previous studies have reported a decrease in E levels after MPA treatment in ciswomen (23, 24). However, this effect may be attributed to MPA's inhibition of the HPG axis and subsequent decline in endogenous estrogen production. In this case, transwomen are unlikely to see large changes in serum E given that their source of estrogen is primarily exogenous.

As expected, we observed a negative correlation between serum testosterone and serum E and a positive correlation between serum E and E dosage in both MPA and non-MPA groups. These findings match those of a previous study done in transwomen treated with E and spironolactone (25).

We found a statistically (but not clinically) significant reduction in Hb and hematocrit (Hct) levels in all regimen groups compared with baseline. A decline in these parameters after GAH therapy is well reported in the literature (26, 27). Furthermore, we found slightly lower Hb and Hct in the MPA group as compared with the non-MPA group at an E dosage of 4 mg. This finding is somewhat divergent from the literature, which reports elevated Hb and Hct in ciswomen after MPA use (28–30). However, these findings may be exclusive to natal females, because elevated Hb and Hct might be consequent to decreased menstrual bleeding (30), a symptom that is absent in transwomen. Moreover, the current study finds that MPA use in transwomen is associated with lower serum testosterone. Depression of this erythropoietic factor may be causal to a decline in Hb and Hct. Studies in a wider cohort should be conducted to confirm the significance of MPA's hematologic effects.

We found a statistically significant elevation in serum prolactin at an E dosage of 6 mg but no change at other dosages. The literature is conflicting on this subject, with some studies suggesting elevated prolactin after feminizing estrogen therapy (31, 32) and others showing a nonsignificant increase (33–35). It is likely that this measure is sensitive to statistical methodology because of interpatient variability. Indeed, we observed that after the Bonferroni correction was eliminated, four more regimen groups displayed significant elevations in prolactin. Within each E dosage level, we found no differences in serum prolactin between MPA and non-MPA groups. This finding is consistent with studies done in postmenopausal women (36), women with breast cancer (37) and endometriosis (38), and women seeking contraception (39, 40). Therefore, although feminizing therapy is often concomitant with elevated prolactin, MPA seems to pose no added risk.

We found no differences between MPA and non-MPA groups in levels of blood glucose, BUN, creatinine, sodium, potassium, chloride, calcium, albumin, bilirubin, ALP, total protein, ALT, or AST. These findings are generally consistent with those of previous studies (38, 41, 42). However, one study found elevated albumin in natal females after MPA treatment, an effect attributed to MPA's interaction with hepatocytes (38). Because testosterone may stimulate these cells (43), the observed reduction in this hormone among MPA-using transwomen might negate potential activation of hepatocytes. Furthermore, MPA was administered in quantities of 100 mg/d in the study, whereas much smaller dosages were used here.

At higher dosages of E, we found significantly reduced albumin, bilirubin, and ALP. There are isolated reports of E-mediated decreases in albumin (44), bilirubin (45), and ALP (46), but literature on the topic is sparse and findings are not universal.

Although this study followed a cohort of transwomen over an extended period of time, there are limitations that should be noted. As mentioned earlier, the incidence of side effects may have been underestimated. Missing data, though attributed mainly to patient refusal and technical issues, may have been a source of selection bias. Finally, this study was not rigorously controlled because of its retrospective nature. Measurements taken during patient FUVs may have been influenced by regimens followed earlier in the course of therapy rather than the regimen closest to the date of the FUV. In addition, dosage of MPA and modality of MPA administration varied between patients. Our findings should be confirmed by well-controlled, prospective studies in a larger cohort.

Another important consideration is the role of spironolactone. In particular, spironolactone is known to interact with the progesterone receptor, thereby interfering with binding of the receptor by MPA and potentially altering the magnitude of MPA's physiological effects. Therefore, interpatient variability in MPA's effects may be explained by differences in levels of spironolactone and sensitivity to this agent between subjects. That is, certain patients may have exhibited altered responsiveness to MPA due to binding of progesterone receptor by spironolactone. Furthermore, we cannot eliminate the possibility of confounding interactions between MPA and spironolactone. For instance, MPA may act as a competitive inhibitor of spironolactone at certain receptors. If spironolactone is known to increase testosterone levels via antagonism of androgen receptor, then inhibition of this process by MPA may decrease testosterone levels. Therefore, the observed decrease in testosterone in the MPA group does not

necessarily imply decreased effector mechanism of this hormone. In sum, the potential effects of spironolactone on androgenic and progestogenic activity should be considered when interpreting our study's results.

Given our discussion of MPA in the context of testosterone suppression, a comparison of MPA with gonadotropin-releasing hormone agonists (GnRHas) is merited. GnRHas are potent antiandrogens often used in puberty suppression that function by desensitizing gonadotropic receptors (47). Although GnRHas are effective inhibitors of testosterone and E synthesis or secretion, usage of this medication in GAH therapy has been limited by its high cost and low insurance coverage (48). Additionally, MPA may be preferred by some patients because of possible enhancement of breast growth, although few studies have thoroughly investigated this subject.

A note about the thrombogenicity of MPA is also warranted. A recent study by Vinogradova *et al.* (49) discerned the VTE risk posed by various hormone replacement therapy regimens in cis women. Among its findings, MPA used in combination with E was associated with greater VTE risk than E alone. In light of this evidence, it may be prudent to closely assess VTE risk in transwomen before and during administration of MPA. That said, the absolute increase in extra VTE events remains small (4/10,000 for E only vs 7/10,000 for E with MPA). Furthermore, the translatability of the quantitative risk assessments by Vinogradova *et al.* to our study sample is unclear, because our mean sample age is significantly lower (31.0 ± 7.1 vs 63.8 ± 11.0 years) and our primary mode of E administration is distinct (sublingual vs oral). Thus, the thrombogenicity of MPA is an important clinical consideration, but the associated risk of VTE in young transwomen is unknown and will probably vary based on sample characteristics.

The transgender population would benefit from more in-depth investigations of MPA. For instance, studies done in cis females have suggested that MPA causes changes in lipid profile and in anthropometric traits such as BMI (42). Moreover, comparative studies of MPA and natural progesterone (prometrium) are needed. Current clinical recommendations are based largely on patient preference or anecdotal evidence, because the relative risks and benefits of MPA and natural progesterone in GAH therapy are unknown. Thus, the transgender population would be well served by future studies such as these described.

Conclusion

Our retrospective study systematically investigated MPA in the context of GAH therapy. We found minimal side effects associated with MPA treatment, unchanged E levels, lower testosterone, and minimal changes in other biochemical parameters. Future studies should be conducted to confirm our findings, systematically assess the safety of MPA, and further investigate the effects of MPA in transgender people.

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Medroxyprogesterone Acetate in Gender-Affirming Therapy for Transwomen: Results from a Retrospective Study

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Is the MPA group and no-MPA group in different or same point of time in their course of treatment? i.e. time on homrone therapy, dosage history, gonadectomy, etc. This is a retrospective study si MPA is not randomly assigned

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