

Supplemental Material

Supplemental Table 1: Search Strategy

Supplemental Table 2: Studies of transgender men on GAHT and creatinine at baseline and follow-up (n=18 studies)

Supplemental Table 3: Studies of transgender women on GAHT and creatinine at baseline and follow-up (n=23 studies)

Supplemental Figure 1: Quality assessment

Supplemental Table 4: Characteristics of creatinine assays of studies included in meta-analysis

Supplemental Table 1: Search Strategy

Medline

| | |
|--|---------|
| gender dysphoria/ or transgender persons/ or "health services for transgender persons"/ or transsexualism/ | 6716 |
| ((gender* or sex*) adj2 (dysphori* or identity disorder*)).ti,ab,kf | 1689 |
| (transgender* or transsexual* or transman or transmen or transwoman or transwomen or transmasculin* or transfeminin* or transpeople* or transperson* or crosssex* or crossgender* or (cross adj sex*) or (cross adj gender*)).ti,ab,kf | 9472 |
| (trans adj5 (gender* or sex* or man or men or woman or women or mascul* or feminin* or people* or person* or male* or female* or individual* or identi* or inclus* or queer* or glbt* or lgbt* or cis or cisgender*)).ti,ab,kf | 25718 |
| or/1-4 | 36478 |
| sex reassignment procedures/ or gender dysphoria/dt or transgender persons/dt or transsexualism/dt | 653 |
| exp hormone replacement therapy/ or feminization/ or exp virilism/ or ((exp gonadal hormones/ or exp hormone antagonists/ or exp pregnanes/ or exp norpregnanes/ or exp gonadotropin-releasing hormone/ or exp azasteroids/ or flutamide/ or letrozole/ or anastrozole/ or exp tamoxifen/ or exp androstanols/) and (tu.fs or th.fs)) | 229160 |
| ((gender* or sex* or crosssex* or crossgender* or affirming or affirmat* or confirming or confirmat* or masculini* or femini* or demasculini* or defemini* or viriliz* or virilis*) adj2 (hormon* or steroid* or treatment or therap* or medicat* or drug*)).ti,ab,kf | 51850 |
| (hormon* or steroid* or abiraterone or aldactone or alora or anastrozole or andractim or andriol or androcur or androderm or androgel or androgen* or androstanolone or antiandrogen* or antiestrogen* or antigonadotropin* or antioestrogen* or arimidex or (aromatase adj2 inhibit*) or axiron or aveed or bazedoxifene or bicalutamide or casodex or chlormadinone or cma or cpa or cyclomen or cyproterone* or danatrol or danazant or danazol or danocrine or delatestryl or delestrogen or desogestrel or dihydrotestosterone or divigel or drospirenone or duavee or duphaston or dutasteride or dydrogesterone or elestrin or elleste or enantone or enzalutamide or equilin or equilenin or estertril or estrace or estradiol* or estroderm or estrofem or estrogen* or estrostep or estrone or ethinylestradiol or etonogestrel or evista or fareston or femara or finasteride or flutamide or galeterone or gestagen* or gestodene or gestogen* or gnhr or goserelin or gynorelle or histrelin or hrt or hydroxyprogesterone or jatenzo or keoxifene or letrozole or leuprolide or leuprorelin or levonorgestrel or lupron or luteran or lynestrenol or medrogestone or medroxyprogesterone or megestrol or mestranol or methandriol or methylandrostenediol or nafarelin or nandrolone or nilutamide or nolvadex or nomegestrol or norethindrone or norethisterone or norgestimate or norgestrel or oestradiol* or oestrogen* or oxandrolone or premarin or primolut or progesteron* or progestagen* or progestogen* or progynova or | 1015632 |

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| promegestone or prometrium or proscar or prostal or provera or raloxifene or (reductase adj2 inhibit*) or serm or serms or spiractin or spironolacton* or stanolone or striant or supprelin or sustanon or synarel* or tamoxifen or testopel or testosterone* or toremifene or triptorelin or vantas or vivelle or xtandi or xyosted or zoladex).ti,ab,kf | |
| or/6-9 | 1162306 |
| 5 and 10 | 3279 |
| exp animals/ not humans.sh | 4734591 |
| (adolescent/ or exp child/ or exp infant/) not exp adult/ | 1885861 |
| (comment or editorial or interview or news or newspaper article).pt | 1474057 |
| 11 not (12 or 13 or 14) | 2678 |

Embase

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|---|--------|
| exp gender dysphoria/ or transsexuality/ or exp transgender/ | 11347 |
| ((gender* or sex*) adj2 (dysphori* or identity disorder*)).ti,ab,kw | 2491 |
| (transgender* or transsexual* or transman or transmen or transwoman or transwomen or transmasculin* or transfeminin* or transpeople* or transperson* or crosssex* or crossgender* or (cross adj sex*) or (cross adj gender*)).ti,ab,kw | 12120 |
| (trans adj5 (gender* or sex* or man or men or woman or women or mascul* or feminin* or people* or person* or male* or female* or individual* or identi* or inclus* or queer* or glbt* or lgbt* or cis or cisgender*)).ti,ab,kw | 28398 |
| or/1-4 | 42446 |
| sex reassignment procedures/ or exp gender dysphoria/dt | 1333 |
| exp hormonal therapy/ or feminization/ or virilization/ or ((exp sex hormone/ or exp sex hormone antagonist/ or pregnane derivative/ or exp gonadorelin derivative/ or azasteroid/ or exp aromatase inhibitor/ or androstane derivative/ or gonadotropin antagonist/ or exp steroid 5alpha reductase inhibitor/ or exp hormone receptor affecting agent/) and (tu.fs or th.fs)) | 330045 |
| ((gender* or sex* or crosssex* or crossgender* or affirming or affirmat* or confirming or confirmat* or masculini* or femini* or demasculini* or defemini* or viriliz* or virilis*) adj2 (hormon* or steroid* or treatment or therap* or medicat* or drug*)).ti,ab,kw | 67652 |

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| (hormon* or steroid* or abiraterone or aldactone or alora or anastrozole or andractim or andriol or androcur or androderm or androgel or androgen* or androstanolone or antiandrogen* or antiestrogen* or antigonadotropin* or antioestrogen* or arimidex or (aromatase adj2 inhibit*) or axiron or aveed or bazedoxifene or bicalutamide or casodex or chlormadinone or cma or cpa or cyclomen or cyproterone* or danatrol or danazant or danazol or danocrine or delatestryl or delestrogen or desogestrel or dihydrotestosterone or divigel or drospirenone or duavee or duphaston or dutasteride or dydrogesterone or elestrin or elleste or enantone or enzalutamide or equilin or equilenin or esterrol or estrace or estradiol* or estroderm or estrofem or estrogel or estrogen* or estrostep or estrone or ethinylestradiol or etonogestrel or evista or fareston or femara or finasteride or flutamide or galeterone or gestagen* or gestodene or gestogen* or gnhr or goserelin or gynorelle or histrelin or hrt or hydroxyprogesterone or jatenzo or keoxifene or letrozole or leuprolide or leuprorelin or levonorgestrel or lupron or luteran or lynestrenol or medrogestone or medroxyprogesterone or megestrol or mestranol or methandriol or methylandrostenediol or nafarelin or nandrolone or nilutamide or nolvadex or nomegestrol or norethindrone or norethisterone or norgestimate or norgestrel or oestradiol* or oestrogen* or oxandrolone or premarin or primolut or progesteron* or progestagen* or progestogen* or progynova or promegestone or prometrium or proscar or prostal or provera or raloxifene or (reductase adj2 inhibit*) or serm or serms or spiractin or spironolacton* or stanolone or striant or supprelin or sustanon or synarel* or tamoxifen or testopel or testosterone* or toremifene or triptorelin or vantas or vivelle or xtandi or xyosted or zoladex).ti,ab,kw | 1270336 |
| or/6-9 | 1468207 |
| 5 and 10 | 5178 |
| (exp animal/ or nonhuman/) not exp human/ | 6432158 |
| (exp adolescent/ or exp child/) not exp adult/ | 2149735 |
| (editorial or note).pt | 1478283 |
| 11 not (12 or 13 or 14) | 4167 |

Cochrane

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|--|-----|
| gender dysphoria/ or transgender persons/ or "health services for transgender persons"/ or transsexualism/ | 65 |
| ((gender* or sex*) adj2 (dysphori* or identity disorder*)).ti,ab,hw | 29 |
| (transgender* or transsexual* or transman or transmen or transwoman or transwomen or transmasculin* or transfeminin* or transpeople* or transperson* or crosssex* or crossgender* or (cross adj sex*) or (cross adj gender*)).ti,ab,hw | 339 |

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|---|--------|
| (trans adj5 (gender* or sex* or man or men or woman or women or mascul* or feminin* or people* or person* or male* or female* or individual* or identi* or inclus* or queer* or glbt* or lgbt* or cis or cisgender*)).ti,ab,hw | 445 |
| or/1-4 | 768 |
| sex reassignment procedures/ or gender dysphoria/dt or transgender persons/dt or transsexualism/dt | 4 |
| exp hormone replacement therapy/ or feminization/ or exp virilism/ or ((exp gonadal hormones/ or exp hormone antagonists/ or exp pregnanes/ or exp norpregnanes/ or exp gonadotropin-releasing hormone/ or exp azasteroids/ or flutamide/ or letrozole/ or anastrozole/ or exp tamoxifen/ or exp androstanols/) and (tu.fs or th.fs)) | 22828 |
| ((gender* or sex* or crosssex* or crossgender* or affirming or affirmat* or confirming or confirmat* or masculini* or femini* or demasculini* or defemini* or viriliz* or virilis*) adj2 (hormon* or steroid* or treatment or therap* or medicat* or drug*)).ti,ab,hw | 9651 |
| (hormon* or steroid* or abiraterone or aldactone or alora or anastrozole or andractim or andriol or androcur or androderm or androgel or androgen* or androstanolone or antiandrogen* or antiestrogen* or antigonadotropin* or antioestrogen* or arimidex or (aromatase adj2 inhibit*) or axiron or aveed or bazedoxifene or bicalutamide or casodex or chlormadinone or cma or cpa or cyclomen or cyproterone* or danatrol or danazant or danazol or danocrine or delatestryl or delestrogen or desogestrel or dihydrotestosterone or divigel or drospirenone or duavee or duphaston or dutasteride or dydrogesterone or elestrin or elleste or enantone or enzalutamide or equilin or equilenin or esterrol or estrace or estradiol* or estroderm or estrofem or estrogel or estrogen* or estrostep or estrone or ethinylestradiol or etonogestrel or evista or fareston or femara or finasteride or flutamide or galeterone or gestagen* or gestodene or gestogen* or gnhr or goserelin or gynorelle or histrelin or hrt or hydroxyprogesterone or jatenzo or keoxifene or letrozole or leuprolide or leuprorelin or levonorgestrel or lupron or luteran or lynestrenol or medrogestone or medroxyprogesterone or megestrol or mestranol or methandriol or methylandrostenediol or nafarelin or nandrolone or nilutamide or nolvadex or nomegestrol or norethindrone or norethisterone or norgestimate or norgestrel or oestradiol* or oestrogen* or oxandrolone or premarin or primolut or progesteron* or progestagen* or progestogen* or progynova or promegestone or prometrium or proscar or prostal or provera or raloxifene or (reductase adj2 inhibit*) or serm or serms or spiractin or spironolacton* or stanolone or striant or supprelin or sustanon or synarel* or tamoxifen or testopel or testosterone* or toremifene or triptorelin or vantas or vivelle or xtandi or xyosted or zoladex).ti,ab,hw | 116351 |
| or/6-9 | 131010 |
| 5 and 10 | 94 |
| exp animals/ not humans.sh | 12 |
| (adolescent/ or exp child/ or exp infant/) not exp adult/ | 57327 |

11 not (12 or 13) 94

Clinicaltrials.gov

hormone OR "hormonal therapy" OR steroid OR abiraterone OR aldactone OR alora OR anastrozole OR andractim OR andriol OR androcur OR androderm OR androgel | transgender OR trans OR "gender dysphoria" OR "gender identity" 78

androgen OR androstanolone OR antiandrogen OR antiestrogen OR antigonadotropin OR antioestrogen OR arimidex OR "aromatase inhibitor" OR axiron OR aveed | transgender OR trans OR "gender dysphoria" OR "gender identity" 18

bazedoxifene OR bicalutamide OR casodex OR chlormadinone OR cma OR cpa OR cyclomen OR cyproterone OR danatrol OR danazant OR danazol OR danocrine | transgender OR trans OR "gender dysphoria" OR "gender identity" 5

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elestrin OR elleste OR enantone OR enzalutamide OR equilin OR equilenin OR esterol OR estrace OR estradiol OR estroderm OR estrofem OR estrogel | transgender OR trans OR "gender dysphoria" OR "gender identity" 28

estrogen OR estrostep OR estrone OR ethinylestradiol OR etonogestrel OR evista OR fareston OR femara OR finasteride OR flutamide | transgender OR trans OR "gender dysphoria" OR "gender identity" 18

galeterone OR gestagen OR gestodene OR gestogen OR gnhr OR goserelin OR gynorelle OR histrelin OR hrt OR hydroxyprogesterone OR jatenzo OR keoxifene | transgender OR trans OR "gender dysphoria" OR "gender identity" 17

letrozole OR leuprolide OR leuprorelin OR levonorgestrel OR lupron OR luteran OR lynestrenol OR medrogestone OR medroxyprogesterone OR megestrol OR mestranol OR methandriol OR methylandrostenediol | transgender OR trans OR "gender dysphoria" OR "gender identity" 7

nafarelin OR nandrolone OR nilutamide OR nolvadex OR nomegestrol OR norethindrone OR norethisterone OR norgestimate OR norgestrel OR oestradiol OR oestrogen OR oxandrolone | transgender OR trans OR "gender dysphoria" OR "gender identity" 34

premarin OR primolut OR progesteron OR progestagen OR progestogen OR progynova OR promegestone OR prometrium OR proscar OR prosta OR provera OR raloxifene OR "reductase inhibitor" | transgender OR trans OR "gender dysphoria" OR "gender identity" 28

serm OR serms OR spiractin OR spironolacton OR stanolone OR striant OR supprelin OR sustanon OR synarel | transgender OR trans OR "gender dysphoria" OR "gender identity" 12

tamoxifen OR testopel OR testosterone OR toremifene OR triptorelin OR vantas OR vivelle OR xtandi OR xyosted OR zoladex | transgender OR trans OR "gender dysphoria" OR "gender identity"

43

Total unique

88

Supplemental Table 2: Studies of transgender men on GAHT and creatinine at baseline and follow-up (n=18 studies)

| Study | Author (year) | Number of transgender men | GAHT type and dose | Age (years) | Creatinine ($\mu\text{mol/L}$) |
|-------|---|---------------------------|---|--|--|
| 1 | Becerra Fernandez ⁴¹ 2016 | 26 | 21 = testosterone esters (250 mg IM q1-2 weeks) 5 = TU 120-160 mg po daily | 30.2 (7.4) | baseline 64.55 \pm 2.65 3-6 months 76.93 \pm 3.54 6-18 months 72.50 \pm 3.54 |
| 2 | Bunck ²⁵ 2006 | 30 | 16 = Testosterone esters (250mg IM q2-3weeks with non-steroidal aromatase inhibitor anastrozole (1 mg/day) 14 = Testosterone esters (250mg IM q2-3weeks with placebo | Placebo (n=14) 34.8 (8.3) Anastrozole (n=16) 37.1 (7.0) | AI baseline* 93.63 \pm 10.42 3 months 95.19 \pm 7.64 |
| 3 | Fernandez ²⁶ 1999 | 19 | Testosterone IM injections (11mg/day) (calculated as injected dose/days between injections) 75% q2 weeks 25% <q2 weekly | mean 27 range: 19-47 | baseline* 91.07 (10.61) |
| 4 | Giltay ²⁷ 1998 | 17 | Testosterone esters (250mg IM q2weeks) | median 22 range: 16-34 | baseline 77 \pm 9 4 months 85 \pm 12 |

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|---|------------------------------|-----|---|--|--|
| 5 | Giltay ²⁸ 2008 | 14 | Testosterone esters (250mg IM q2weeks) | mean 23.0 (4.2) | baseline 77±9 4 months 85±13 12 months 91±11 |
| 6 | Humble ²⁹ 2019 | 150 | 133 = IM testosterone 3 = transdermal testosterone 14 = IM/transdermal testosterone *Doses not reported | mean 24.2 ± 6.3 years | n=25 baseline 0.77±0.10 6 months 0.9±0.12 n=15 baseline 0.77±0.12 12 months 0.89±0.13 |
| 7 | Kurahashi ³² | 160 | “low dose” 107= testosterone 125mg IM q2 weeks “middle dose” 21= testosterone 250mg IM q3 weeks “high dose” 32= testosterone 250mg IM q2 weeks | mean “low dose” 24.9 ± 0.5, “middle dose” 26.1 ± 1.2 “high dose” 28.1 ± 1.0 | Not reported |

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| 8 | Meriggiola ³³ 2018 | 15 | <p>Prior to study: testoviron depot injections 100mg/q7-15 days = testosterone enanthate 110 mg + testosterone propionate 25 mg.</p> <p>In study:</p> <p>a) TU (1000 mg IM) b) TU (1000 mg IM) + letrozole (2.5mg po daily) c) TU (1000 mg IM) + dutasteride (0.5mg po daily)</p> <p>Injections at 0,6,18,30, 42 weeks</p> | <p>mean</p> <p>a) 34.4 (4.39) b) 36.0 (4.58) c) 36.6 (5.86)</p> | <p>a) only baseline* 87.54±14.15 week 54 90.19±13.26</p> |
| 9 | SoRelle ³⁶ 2019 | Baseline: 62 Post-GAHT: 89 | <p>87= testosterone cypionate 35-300 mg IM q1-2 weeks 1= transdermal testosterone 1= both</p> | <p>mean</p> <p>Baseline: 27 (9) Post-GAHT: 30 (9)</p> | <p>baseline 65.43 GAHT (≥6 months 79.58</p> |
| 10 | van Caenegem ⁴⁴ 2012 | 50 | <p>35 = testosterone esters 30-100mg IM q2-3weeks 7 = TU 1000 mg IM q12 weeks 8 = transdermal testosterone 50 mg daily 1 = oral TU 40 mg po daily and testosterone gel 50 mg daily</p> | <p>mean</p> <p>26 (7)</p> | <p>baseline* 0.93 (0.13)</p> |

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| 11 | van Kesteren ³⁷ 1998 | 19 | 12=testosterone esters 250mg IM q2-3 weeks 7=TU (160mg/daily) | mean 25.0 range 16-39 | baseline 72±8 12 months 79±9 25.2 ± 10.4 months after surgery 85±6 |
| 12 | van Velzen ¹⁷ 2019 | 188 | Ghent: TU 1000mg IM q12 weeks Netherlands: testosterone gel 50mg/daily or testosterone esters 250mg IM q2 weeks | mean 26.4 (9.1) | baseline 67±10 12 months 17.65% (15.0%, 20.3%) 78.79 |
| 13 | Vita ³⁸ 2018 | 11 | 10= testosterone enathate IM q2-4 weeks 1 = TU IM q2-4 weeks *No dose reported | mean 25.1 (3.7) | baseline 61.9±8.8 follow- up (unspecified) 88.4±8.8 |
| 14 | Vlot ¹⁸ 2019 | 132 | testosterone gel 50mg topically daily testosterone esters 250mg IM q2-3weeks TU 1000mg IM q12weeks lynestrenol | median 24 (21-33) | baseline 66±10 12 months 79±12 |
| 15 | Wierckx ⁴⁵ 2012 | 50 | 35= testosterone esters 250 mg IM q2-3 weeks 15= TU 1000 mg IM q12 weeks 7 = testosterone gel 50 mg topically daily 1 = TU 40mg po daily and = testosterone gel 50 mg topically daily | mean 37 (8.2) | baseline* 79.58 (79.58- 88.42) |

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| 16 | Wierckx ¹⁹ 2014 | 53 | TU 1000 mg IM at baseline, 6 weeks, q12 weeks testosterone esters (30-100mg IM q2 weeks) if any intolerance Progestagens | mean Ghent (n=27): 27.3 (8.5) Oslo (n=26): 21.7 (5.1) | baseline 65.43±8.84 12 months 74.27±8.84 |
| 17 | Yahyaoui 2008 ³⁹ | 47 | 1 st year 93.3% testosterone enanthate or propionate 250mg IM q2 weeks 6.7% testosterone patch 5mg topically/day 2 nd year 69.6% testosterone enanthate or propionate 30.5% testosterone patch/gel | mean 25.7 (6.0) | baseline 68.97 (9.73) 12 months 80.46 (13.26) 24 months 78.69 (11.49) |
| 18 | Scharff 2019 ⁴⁶ | 278 | 52 testosterone gel 50 mg daily 130 testosterone esters 250 mg IM q2-3 weeks 81 testosterone undecanoate 1000 mg IM q12 weeks | median (IQR) 23 (20-30) | baseline 66.0 (9.0) 12 months 77.4 (10.6) |

Note: GAHT=gender-affirming hormone therapy, IM=intramuscular, testosterone undecanoate = TU

*Indicates “baseline” at the start of study for patients already on GAHT

Supplemental Table 3: Studies of transgender women on GAHT and creatinine at baseline and follow-up (n=23 studies)

| Study | Author (year) | Number of transgender women | GAHT type and dose | Age (years) | Creatinine (µmol/L) |
|-------|---|-----------------------------|--|-----------------------------|---|
| 1 | Angus ⁴⁰ 2019 | 80 | 21 = estradiol alone, estradiol valerate (6mg (4,6)) 21 = estradiol and CPA (50mg (25, 50)) 38 = estradiol and spironolactone (100mg (87.5–200)) | median 27 (22–45) | baseline* estradiol alone 78 (72–96) CPA 72 (63–75) spironolactone 77 (69–85) |
| 2 | Becerra Fernandez ⁴¹ 2016 | 31 | 27 = estrogen enanthate (100-200mg q monthly IM) 27 = progesterone (algestone) (150mg/10mg of estrogen q monthly IM) 27= CPA (200-400mg) 4 = other combinations | mean 30.2 (7.4) | baseline* 88.42 (15.92) |
| 3 | Cottrell ⁴² 2019 | 4 | 4 = estrogen 1 = progesterone 4 = spironolactone *Doses not reported | median 42 (34, 46) | Not reported |
| 4 | Fernandez ²⁶ 1999 | 33 | Oral estrogen 18, 7 (1.44 mg/day, 1.71 mg/day) Estrogen patch 7, 2 (0.1 mg/day, 0.1 mg/day) Estrogen injection 7, 5 (1.21 mg/day, 1.18 mg/day) Spironolactone 23, 14 (104 mg/day, 114 mg/day) | mean 31 range: 16-56 | baseline 64.55±2.65 3-6 months 76.93±3.54 6-18 months 50±3.54 |
| 5 | Giltay ²⁷ 1998 | 17 | ethinyl estradiol 100ug/day CPA100mg/day | median 28 range 18–40 | baseline 86±8 4 months 79±9 |

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|----|-------------------------------------|-----|--|------------------------|--|
| 6 | Giltay ²⁸ 2008 | 15 | ethinyl estradiol 100ug/day CPA 100mg/day | mean 26.3 (6.3) | baseline 84±8 4 months 77±10 12 months 76±8 |
| 7 | Hiransuthikul ³⁰ 2019 | 20 | E2 valerate 2mg/day CPA 25mg/day | median 21.5 (21–26) | Not reported |
| 8 | Humble ²⁹ 2019 | 152 | 58=oral estrogen 2=IM estrogen 43=transdermal estrogen 3=oral/IM estrogen 38=oral/transdermal estrogen 2=IM/transdermal estrogen 6=oral/IM/transdermal estrogen 144=spironolactone *Doses not reported | mean 31.8 (12.5) | n= 66 baseline 0.92±0.14 mEq/L 6 months 0.91(±0.16) mEq/L n = 49 baseline 0.93±0.15 mEq/L 12 months 0.89±0.15 mEq/L |
| 9 | Jain ³¹ 2019 | 92 | 39 patients receiving MPA 53 patients not receiving MPA sublingual E (2-12 mg daily) spironolactone= 100-200 mg/daily) MPA= 5-10mg sl daily/150 mg IM q3 months Table 1 for estrogen doses | mean 31.0 (7.1) | baseline* 77.81±12.38 3 months results varied by dose of MPA |
| 10 | Nicholls ³⁴ | 22 | 21= stilboestrol 5-40mg/day 1 = ethinylestradiol 0.4mg daily | range 19-55 | Not reported |
| 11 | Roberts ⁴³ 2014 | 55 | Not reported | Not reported | baseline* 0.55-1.3 |

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|----|------------------------------------|-----|--|--------------------------|---|
| 12 | Shieh ³⁵ 2019 | 8 | 3 estradiol (oral) (2-6mg daily) 5 estradiol valerate (IM) (0.5-40mg IM q 1-2 weeks) 3 premarin (1.25-6.25mg daily) 6 spironolactone (50-200mg daily) 1 medroxyprogesterone (5mg daily) | median 29 (26, 41) | baseline not reported Day 7 0.80 (0.80, 0.88) |
| 13 | SoRelle ³⁶ 2019 | 133 | 112 oral estradiol 12 estradiol valerate 3 transdermal estradiol 6 other estrogens 107 spironolactone 1 CPA Doses in supplemental Table 1 | mean 33 | baseline 86.65 GAHT ≥6 months 76.04 |
| 14 | van Kesteren ³⁷ 1998 | 20 | CPA (100mg/daily) ethinyl oestradiol (100 mcg/daily) after surgery: 15=ethinyl oestradiol 1-2 50mcg per day 4=conjugated estrogens 1=transdermal oestradiol | mean 25.4 | baseline 81±7 12 months 77±7 25.2 ± 10.4 months after surgery 78 ±7 |
| 15 | van Velzen ¹⁷ 2019 | 242 | CPA 50mg/daily 144: estradiol valerate 2 mg/ 2x day if <45 years 98: estradiol patches 100ug/24hrs if >45 years | mean (SD) 32.3 (12.6) | baseline 77±10 12 months 5.3%, (-6.5, -4.1 change) 72.92 |
| 16 | Vita ³⁸ 2018 | 21 | oral estradiol (estradiol valerate (2-6mg/d), CPA (50-100 mg/d) progesterone Only estradiol after sex reassignment surgery | mean 25.2 (7.0) | baseline 70.7±8.8 follow-up (unspecified) 70.7±8.8 |

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|----|--------------------------------|-----|---|--|---|
| 17 | Vlot ¹⁸ 2019 | 121 | CPA (50-100mg/daily) estradiol valerate (2-4mg/daily) estradiol patches (50-100ug/24hours 2x/week) | median 24 (IQR 21-33) | baseline 77±10 12 months 73±10 |
| 18 | Wierckx ⁴⁵ 2012 | 50 | CPA 50-100mg/daily 22=transdermal estradiol 1.5mg/day 3=estradiol patch 50mcg/day 19=estradiol valerate 2mg daily 1=estriol 2mg daily | mean 43.0 (10.4) | baseline* 70.74 (61.89 - 79.58) N/A |
| 19 | Wierckx ¹⁹ 2014 | 53 | N=40 (<45 years) CPA (50mg/daily) estradiol valerate (4mg/daily) N=13 (>45 years) CPA (50mg/daily) transdermal 17-B estradiol patch (100mcg/24 hours) | Ghent (n=47) mean 31.7 (14.8) Oslo (n=6) mean 19.3 (2.4) | a) Oral Estrogen baseline 79.58±8.84 12 months 70.74±8.84 b) Transdermal estrogen baseline 82.23±8.84 12 months 75.16±8.84 |
| 20 | Yahyaoui ³⁹ 2008 | 22 | CPA 50-100mg 18 conjugated oral estrogens 1 oral estradiol valerate 3 transdermal estradiol patches 16 low, 6 medium, 0 high doses respectively | mean 23.1 (9.4) | baseline 79.58 (15.03) 12 months 74.27 (18.57) 24 months 68.97 (18.57) |
| 22 | Scharff 2019 ⁴⁶ | 249 | CPA 50mg daily 134=2-4 mg oral estradiol valerate a day 86=100 µg/24 h estradiol patch twice a week | median (IQR) 28 (23-40) | baseline 78.5 (10.8) 12 months 73.1 (10.6) |

| | | | | | |
|----|------------------------------|----|---|--|---|
| 23 | Giltay 2003 ⁴⁷ | 40 | 10=CPA 100 mg/day 15 =CPA 100 mg/day + oral ethinyl estradiol 100 mg/day 15 =CPA 100 mg/day + transdermal 17b-estradiol | mean 34 years, range 19-50 mean 33 years, range 20-43 age 31 years, range 20-44 | Baseline 90 (11) 2 months 91 (8) 4 months 87 (8) Baseline 89 (9) 2 months 86 (9) 4 months 87 (8) |
|----|------------------------------|----|---|--|---|

Note: GAHT=gender-affirming hormone therapy, CPA=cyproterone acetate, MPA = medroxyprogesterone acetate

*Indicates “baseline” at the start of study for patients already on GAHT

| | Fernandez | Giltay 1998 | Giltay* 2003 | Humble | Scharff | Sorelle | van Kesteren | Vita | Yahyaoui |
|--|-----------|-------------|--------------|--------|---------|---------|--------------|------|----------|
| 1. Study question | | | | | | | | | |
| 2. Eligibility criteria and study population | | | | | | | | | |
| 3. Generalizability | | | | | | | | | |
| 4. All eligible participants enrolled | | | | | | | | | |
| 5. Sample size | | | | | | | | | |
| 6. Intervention clearly described | | | | | | | | | |
| 7. Outcome measures clearly described, valid and reliable | | | | | | | | | |
| 8. Blinding of outcome assessors | | | | | | | | | |
| 9. Follow-up rate | | | | | | | | | |
| 10. Statistical analysis | | | | | | | | | |
| 11. Multiple outcome measures | | | | | | | | | |
| 12. Group-level interventions and individual-level outcome efforts | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Quality rating | Fair | Fair | Fair | Fair | Fair | Fair | Poor | Poor | Fair |

Supplemental Figure 1: Quality assessment

Note: *randomized controlled trial, NA= not applicable



Low risk of bias



High risk of bias



Cannot determine/
Not reported

Supplemental Table 4: Characteristics of creatinine assays of studies included in meta-analysis

| Study | Author (year) | Creatinine assay |
|-------|-----------------------------------|---|
| 1 | Fernandez ²⁶ (2016) | Not reported |
| 2 | Giltay ⁴⁶ (2003) | Not reported |
| 3 | Giltay ²⁷ (1998) | Not reported |
| 4 | Humble ²⁹ (2019) | Roche Modular P Roche Modular E170 Cobas 8000 system (c502, c602, e702) |
| 5 | SoRelle ³⁶ (2019) | Roche Cobas |
| 6 | Scharff ⁴⁷ (2019) | Not reported |
| 7 | van Kesteren ³⁷ (1998) | Not reported |
| 8 | Vita ³⁸ (2018) | Not reported |
| 9 | Yahyaoui ³⁹ (2008) | Colorimetric enzymatic method |