Effectiveness of Pharmacological Intervention among Men with Infertility: A systematic review and network meta-analysis

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### APPENDIX I: SEARCH STRATEGY

#### Search Term

| Search Term                                                                 | PubMed | Scopus | Cochrane Library | Embase | EBSCOhost | Ovid Medline | Google Scholar |
|-----------------------------------------------------------------------------|--------|--------|------------------|--------|-----------|--------------|----------------|
| "infertility"[MeSH Terms] OR "infertility"[All Fields]] AND ("oligospermia"[MeSH Terms] OR "oligospermia"[All Fields]) AND "humans"[MeSH Terms] | Result 5535 8200 207 4733 3049 | 4777 15 | | | | | |
| Chosen 5499 4786 69 1810 403 4301 | | | | | | | |
| "infertility"[MeSH Terms] OR "infertility"[All Fields]) AND ("azoospermia"[MeSH Terms] OR "azoospermia"[All Fields] OR "azospermia"[All Fields]) AND "humans"[MeSH Terms] | Result 4709 352 18 6523 | 3705 8351 80 | | | | | |
| Chosen 2352 173 14 2212 641 4375 | | | | | | | |
| ("infertility"[MeSH Terms] OR "infertility"[All Fields]) AND ("oligospermia"[MeSH Terms] OR "oligospermia"[All Fields] OR "oligozoospermia"[All Fields]) AND "humans"[MeSH Terms] | Result 5992 5288 61 | 1494 1137 2672 15 | | | | | |
| Chosen 236 2316 10 115 2212 641 | | | | | | | |
| ("infertility"[MeSH Terms] OR "infertility"[All Fields]) AND ("oligospermia"[MeSH Terms] OR "oligospermia"[All Fields] OR "oligoasthenoteratozoospermia"[All Fields]) AND "humans"[MeSH Terms] | Result 5677 1241 38 434 | 271 707 6 | | | | | |
| Chosen 236 2316 10 115 2212 641 | | | | | | | |
| ("infertility"[MeSH Terms] OR "infertility"[All Fields]) AND ("semen"[MeSH Terms] OR "semen"[All Fields]) AND "humans"[MeSH Terms] | Result 10225 41244 876 | 13428 11509 21294 373 | | | | | |
| Chosen 7123 22701 322 4288 1307 12591 257 | | | | | | | |
| ("infertility"[MeSH Terms] OR "infertility"[All Fields]) AND ("oligospermia"[MeSH Terms] OR "oligospermia"[All Fields] OR "oligoasthenoteratozoospermia"[All Fields]) AND "humans"[MeSH Terms] | Result 6036 7319 79 | 143 239 483 3 | | | | | |
| Chosen 161 4161 20 33 1 181 2 | | | | | | | |
| ("infertility"[MeSH Terms] OR "infertility"[All Fields]) AND ("azoospermia"[MeSH Terms] OR "azoospermia"[All Fields] OR "azospermia"[All Fields]) AND "humans"[MeSH Terms] | Result 5521 1224 29 | 318 135 402 0 | | | | | |
| Chosen 0 26 2 28 1 23 0 | | | | | | | |
| ("infertility"[MeSH Terms] OR "infertility"[All Fields]) AND ("oligospermia"[MeSH Terms] OR "oligospermia"[All Fields] OR "oligoasthenoteratozoospermia"[All Fields]) AND "humans"[MeSH Terms] | Result 5993 1119 29 | 93 52 333 3 | | | | | |
| Chosen 1 7 0 4 3 2 2 | | | | | | | |
| ("infertility"[MeSH Terms] OR "infertility"[All Fields]) AND ("oligospermia"[MeSH Terms] OR "oligospermia"[All Fields] OR "oligoasthenoteratozoospermia"[All Fields]) AND "humans"[MeSH Terms] | Result 5677 317 1 | 30 17 95 0 | | | | | |
| Chosen 0 2 0 4 0 0 0 | | | | | | | |
| Condition                                                                 | Result  | Chosen |
|--------------------------------------------------------------------------|---------|--------|
| "infertility"[MeSH Terms] OR "infertility"[All Fields] AND ("genitalia"[MeSH Terms] OR "genitalia"[All Fields] OR "genital"[All Fields]) AND ("disease"[MeSH Terms] OR "disease"[All Fields]) | 4162    | 780    |
| "infertility"[MeSH Terms] OR "infertility"[All Fields] OR "subfertility"[All Fields] AND ("genitalia"[MeSH Terms] OR "genitalia"[All Fields] OR "genital"[All Fields]) AND ("disease"[MeSH Terms] OR "disease"[All Fields]) | 11781   | 1552   |
| "infertility"[MeSH Terms] OR "infertility"[All Fields] OR "subfertility"[All Fields] AND ("genitalia"[MeSH Terms] OR "genitalia"[All Fields] OR "genital"[All Fields]) AND ("disease"[MeSH Terms] OR "disease"[All Fields]) | 6508    | 321    |
| Subfertile[All Fields] AND ("oligospermia"[MeSH Terms] OR "oligospermia"[All Fields]) | 167     | 49     |
| Subfertile[All Fields] AND ("azoospermia"[MeSH Terms] OR "azoospermia"[All Fields] OR "azospermia"[All Fields]) | 107     | 10     |
| Subfertile[All Fields] AND ("oligospermia"[MeSH Terms] OR "oligospermia"[All Fields] OR "oligozoospermia"[All Fields]) | 189     | 1     |
| Subfertile[All Fields] AND ("oligospermia"[MeSH Terms] OR "oligospermia"[All Fields] OR "oligoasthenoteratozoospermia"[All Fields]) | 177     | 0     |
| Subfertile[All Fields] AND ("genitalia"[MeSH Terms] OR "genitalia"[All Fields] OR "genital"[All Fields]) AND ("disease"[MeSH Terms] OR "disease"[All Fields]) | 65      | 7      |
| Subfertile[All Fields] AND ("semen"[MeSH Terms] OR "semen"[All Fields]) | 747     | 131    |
| Subfertile[All Fields] AND ("oligospermia"[MeSH Terms] OR "oligospermia"[All Fields] OR ("low"[All Fields] AND "sperm"[All Fields] AND "count"[All Fields]) OR "low sperm count"[All Fields]) | 224     | 0      |
Supplementary Table 1: Reasons for study exclusion after full-text assessment (n=607)

| Database                                                                 | Number of records |
|-------------------------------------------------------------------------|-------------------|
| Review articles                                                         | 203               |
| Irrelevant articles (conference papers/proceedings, letter to the editor and study protocols) | 194               |
| Meta-Analysis                                                           | 19                |
| Surgical intervention articles                                          | 30                |
| Systematic reviews                                                     | 44                |
| Does not meet selection criteria (details are as under)-                | 75                |
| Not measured male patient data                                          | 37                |
| Not measured the selected outcomes                                      | 51                |
**Supplementary Figure 1:** Overall meta-analysis for sperm concentration of included RCTs (n=29)

| Study or Subgroup | Intervention Mean | Placebo Mean | Mean Difference | Risk of Bias |
|------------------|------------------|-------------|-----------------|--------------|
| 10 Michi 1985    | 7.62             | 3.02        | 4.60            | A            |
| 14 Amiak 1987    | 0.68             | 24.33       | -23.65          | C            |
| 19a A. Nadizadeh 2012 | 17.47          | 13.06       | 4.41            | D            |
| 22 Abdul Razzaq 2014 | 23            | 18.73       | 4.20            | E            |
| 22a Nicola Cojocaru 2012 | 3.8            | 3.84        | 0.00            | F            |
| 23a Martin Imhoff 2012 | 13.5           | 15.21       | -1.71           | G            |
| 24a Mohammad Reza Safarinejad 2012 | 28.7           | 4.6        | 24.10           | A            |
| 25 Pusch 1984    | 6.75             | 14.56       | -7.81           | A            |
| 26 Mahanoud Hussein 2012 | 2              | 17          | 15              | A            |
| 29a A. Nadizadeh 2011 | -0.04          | 11.05       | 11.09           | A            |
| 31a Hussein Ogunm 2009 | 7.8            | 13.42       | -5.60           | A            |
| 33a Murad 2001   | 5.1              | 20.1        | -15.0           | A            |
| 33a Murad 2001   | 7.6              | 27.85       | -20.2           | A            |
| 33a Murad 2001   | -0.4             | 18.34       | 17.94           | A            |
| 34a Mohammad Reza Safarinejad 2019 | 6.2            | 4.5         | 1.70            | A            |
| 38a RobertsPard 2003 | 8.5            | 9.01        | -0.50           | A            |
| 41a Andrea et 2003 | 4.92            | 7.92        | -3.01           | A            |
| 44a Efros Carri 2003 | 2.5            | 5.73        | 3.23            | A            |
| 45a Dimihibis 2003 | 34.4           | 295.56      | -261.16         | A            |
| 46a Wei Yee Yong 2002 | 4              | 140.73      | -136.70         | A            |
| 46a Wei Yee Yong 2002 | 4.5            | 190.81      | -186.30         | A            |
| 46a Wei Yee Yong 2002 | 4.5            | 85.99       | -81.40          | A            |
| 47a Carlo Foresta 2002 | 4.5            | 3.14        | 1.38            | A            |
| 47a Carlo Foresta 2002 | 2.1            | 2.31        | 0.20            | A            |
| 50a A. Kamiske 1998 | 1.2             | 10.52       | -9.30           | A            |
| 59a C. Kekke 1994 | 24              | 94.44       | -70.44          | A            |
| 63a V. KRAUJE 1992 | 2.1             | 12.92       | -10.81          | A            |
| 67a Yin man Eng 2015 | 1.7             | 6.05        | -4.35           | A            |
| 67a Yin man Eng 2015 | 1.6             | 3.38        | -1.78           | A            |
| 67a Yin man Eng 2015 | 1.4            | 9.01        | -7.60           | A            |
| 67a Yin man Eng 2015 | 10.1            | 6.44        | 3.68            | A            |
| 72a Milt 2015    | 3.58             | 2.21        | 1.39            | A            |
| 72a Milt 2015    | 1.76             | 2.04        | -0.28           | A            |
| 72a Milt 2015    | 3.23             | 2.57        | 0.66            | A            |
| 74a Matus Tijh 2016 | 5.7             | 20.48       | -14.65          | A            |
| 76a A. FARRE 2015 | 3.74            | 6.89        | -3.15           | A            |
| 77a R. Sale 2010 | 8.6             | 11.3        | -2.74           | A            |
| 78a R. Parad 2013 | 13.4            | 7.5         | 5.90            | A            |
| 80a Tinkov 2020   | 45              | 62.42       | -17.40          | A            |
| 80a Tinkov 2020   | 38              | 112.44      | -74.40          | A            |
| 80a Tinkov 2020   | 46              | 160.06      | -114.00         | A            |
| 80a Tinkov 2020   | 43              | 242.42      | -199.00         | A            |

**Total (95% CI):** 5997 100.00% 4.00 [3.54, 6.26]

**Heterogeneity:** I^2 = 11.31, Chi^2 = 33.44, df = 41 (P < 0.0001), I^2 = 6.1%

**Test for overall effect:** Z = 7.05 (P < 0.0001)

**Risk of bias assessed:**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Selective reporting (reporting bias)
(D) Other bias
(F) Blinding of participants and personnel (performance bias)
(G) Blinding of outcome assessment (detection bias)
Supplementary Figure 2: Overall meta-analysis for sperm motility of included RCTs (n=29)
Supplementary Figure 3: Overall meta-analysis for sperm morphology of included RCTs (n=29)
Supplementary Figure 4: Sub-group meta-analysis (intervention based) for sperm concentration (n=29)

| Study or Subgroup | Intervention Mean | SD | Teal | Mean | SD | Teal | Weight | Mean Difference | IV, Random | 95% CI | Year | Mean Difference | IV, Random | 95% CI | Risk of Bias |
|-------------------|------------------|----|------|------|----|------|--------|----------------|------------|-------|------|----------------|------------|-------|-------------|
| 1.3.2 SERM        |                  |    |      |      |    |      |        |                |            |       |      |                |            |       |             |
| 10 Miki 1986      | 7.52             | 3.62| 36   | 0.72| 3.18| 15   | 4.1%   | 6.30 [5.57, 7.23] | 1985       |        |      |                |            |       |             |
| 14 Miki 1989      | 8.06             | 2.43| 16   | 1.4  | 24.24| 6    | 6.3%   | -0.72 [-1.155, 0.11] | 1987       |        |      |                |            |       |             |
| 23a W. H. PALE 1992 | 2.1  | 0.93| 39   | 0.2  | 9.09| 17   | 2.8%   | 1.90 [-0.89, 6.68] | 1992       |        |      |                |            |       |             |
| 33a Muller 2006   | 7.6              | 2.76| 31   | 0.1  | 13.42| 51   | 1.1%   | 7.50 [-265, 18.58] | 2006       |        |      |                |            |       |             |
| 33b Mural 2006    | -0.6             | 1.84| 30   | 0.1  | 13.42| 51   | 1.5%   | -0.50 [-1.78, 0.71] | 2006       |        |      |                |            |       |             |
| 33c Mural 2006    | 1.1              | 2.81| 12   | 0.1  | 13.42| 51   | 1.3%   | 5.01 [449, 14.98] | 2006       |        |      |                |            |       |             |
| 31a Husseini et al 2003 | 7.8 | 13.42| 30   | 0.7 | 7.97 | 10   | 2.5%   | 7.10 [615, 126.09] | 2003       |        |      |                |            |       |             |
| 72a Milaj 2015    | 3.23             | 2.57| 15   | -2.4| 2.72 | 19   | 4.1%   | 5.63 [3.39, 7.86] | 2015       |        |      |                |            |       |             |
| 72b Milaj 2015    | 5.26             | 2.61| 34   | -2.4| 2.72 | 19   | 4.1%   | 5.96 [7.74, 12.32] | 2015       |        |      |                |            |       |             |

Heterogeneity: $I^2 = 0.02$, $H^2 = 0.08$, df = 8, (P = 0.43), $P = 15$
Test for overall effect: Z = 16.26 (P < 0.0001)

1.3.3 Hormone
25 Phool 1988
50a Akramosha 1989
47a Carlo Foletta 2002
44a Carlo Foletta 2003
45a Dimitriou 2003
39a Robertso 2006
47a R. Bolte 2010
29a Nicola Cucci 2012
78a R. Parodi 2013
67a Yim Men-Don 2015
78a Yim-mian Dong 2015
78a Yim-mian Dong 2015
78a Yim-mian Dong 2015
78a Yim-mian Dong 2015
78a Yim-mian Dong 2015
78a A. F. ABG 2015

Heterogeneity: $I^2 = 8.90$, $H^2 = 10.47$, df = 14, (P = 0.0001), $P = 0.97$
Test for overall effect: Z = 4.40 (P < 0.001)

1.3.6 Vitamins
48a Wal Yee Wong 2002
90a Tinkofildsen 2020
90a Tinkofildsen 2020
90a Tinkofildsen 2020
90a Tinkofildsen 2020
90a Tinkofildsen 2020

Heterogeneity: $I^2 = 0.00$, $H^2 = 0.08$, df = 3, (P = 0.99), $P = 0.05$
Test for overall effect: Z = 0.91 (P = 0.36)

1.3.7 Enzymes
9a C. H. A. 1994

Heterogeneity: not applicable
Test for overall effect: Z = 0.13 (P = 0.90)

1.3.8 Supplements
48a Wal Yee Wong 2002
48a Wal Yee Wong 2002
41a Andrea Ito 2004
34a Mohammad Reza Bariainzadeh 2000
26a A. Nasiriabadipour 2010
24a Mohammad Reza Baraminzadeh 2010
23a Meritum Intan 2012
19a A. Nasiriabadipour 2012
26 Mahdonz Heppen 2012
28a A. Ito 2012
74a Marnix Lipca 2016
22 Abdul Razzaq 2018
90a Tinkofildsen 2020

Heterogeneity: $I^2 = 20.00$, $H^2 = 12570$, df = 12, (P = 0.0000), $P = 91$
Test for overall effect: Z = 3.71 (P = 0.003)

Total (95% CI) 252
Heterogeneity: $I^2 = 11.31$, $H^2 = 32509$, df = 41, (P = 0.0000), $P = 87$
Test for overall effect: Z = 7.95 (P = 0.0001)
Test for subpop differences: $I^2 = 3.71$, df = 4 (P = 0.44), $P = 99$
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Selective reporting (reporting bias)
(D) Other bias
(E) Blinding of participants and personnel (performance bias)
(F) Blinding of outcome assessment (detection bias)
(G) Incomplete outcome data (attrition bias)
**Supplementary Figure 5:** Sub-group meta-analysis (SERM type based) for sperm concentration (n = 6).

| Study or Subgroup | Intervention | Placebo | Mean Difference | Risk of Bias |
|-------------------|-------------|---------|-----------------|--------------|
| Mean | SD | Total | Mean | SD | Total | IV, Random 95% CI | Mean Difference | IV, Random 95% CI | A | B | C | D | E | F | G |
| 1.7.1 Tamoxifen | 0.68 | 24.33 | 16 | 1.4 | 24.24 | 16 | 0.2% | -0.72 [17.55; 16.11] | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| 33a Murat 2016 | 7.6 | 27.65 | 31 | 0.1 | 13.42 | 25 | 0.4% | 7.50 [3.56; 19.58] | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| 33a Murat 2016 | -1.4 | 18.34 | 30 | 0.1 | 13.42 | 25 | 0.7% | -0.50 [1.89; 7.91] | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| 33a Murat 2016 | 3.1 | 28.1 | 42 | 0.1 | 13.42 | 25 | 0.5% | 5.00 [-4.96; 14.98] | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| 63 a W. KRAISE 1992 | 2.1 | 12.82 | 39 | 0.2 | 8.09 | 37 | 2.3% | 1.90 [2.69; 6.69] | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| 72a Milat 2015 | 323 | 25.7 | 45 | -2.4 | 2.72 | 29 | 32.6% | 5.63 [4.39; 6.87] | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| 72a Milat 2015 | 358 | 2.21 | 34 | -2.4 | 2.72 | 29 | 32.9% | 5.98 [4.74; 7.22] | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Subtotal (95% CI) | 237 | 166 | 69.6% | 5.61 [4.75; 6.46] | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |

Heterogeneity: Tau^2 = 0.00; Chi^2 = 1.34, df = 6 (P = 0.50), I^2 = 0%

Test for overall effect: Z = 12.91 (P < 0.00001)

1.7.2 Clomiphen

| Study or Subgroup | Intervention | Placebo | Mean Difference | Risk of Bias |
|-------------------|-------------|---------|-----------------|--------------|
| Mean | SD | Total | Mean | SD | Total | IV, Random 95% CI | Mean Difference | IV, Random 95% CI | A | B | C | D | E | F | G |
| 10 Milici 1986 | 782 | 36.2 | 56 | 1.72 | 3.18 | 45 | 28.7% | 6.90 [5.57; 8.23] | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| 31a Hussein Khanem 2009 | 7.8 | 13.42 | 30 | 0.7 | 7.97 | 30 | 1.7% | 7.10 [1.51; 12.69] | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Subtotal (95% CI) | 86 | 75 | 30.4% | 6.91 [5.62; 8.20] | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |

Heterogeneity: Tau^2 = 0.00; Chi^2 = 1.00, df = 1 (P = 0.95), I^2 = 0%

Test for overall effect: Z = 10.49 (P < 0.00001)

Risk of bias legend:
- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Selective reporting (reporting bias)
- (D) Other bias
- (E) Blinding of participants and personnel (performance bias)
- (F) Blinding of outcome assessment (detection bias)
- (G) Incomplete outcome data (attrition bias)
Supplementary Figure 6: Sub-group meta-analysis (Supplement type based) for sperm concentration (n = 12)
Supplementary Figure 7: Sub-group meta-analysis (intervention based) for sperm motility (n = 29)
Supplementary Figure 8: Sub-group meta-analysis (SERM type based) for sperm motility (n = 6).
### Supplementary Figure 9: Sub-group meta-analysis (supplement type based) for sperm motility (n = 12).

| Study or Subgroup | Intervention | Placebo | Mean Difference | Risk of Bias |
|-------------------|--------------|---------|-----------------|--------------|
|                  | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI |  |
| 1.16.4 Zinc Sulfate | 22 Abdul Razzaq 2019 | 18 | 12.29 | 80 | 0 | 9 | 60 | 10.5% | 19.00 [14.15, 21.85] | ? |
|                   | 26 Mahonem Russem 2012 | 16 | 7.55 | 37 | 0 | 7 | 37 | 10.9% | 16.00 [12.68, 19.32] | ? |
|                   | 46a Vai Yee Vong 2002 | 6 | 80.66 | 23 | 0 | 89.59 | 26 | 0.5% | 5.00 [13.14, 53.14] | ? |
|                   | 46b Vai Yee Vong 2002 | 2 | 86.29 | 24 | 0 | 89.59 | 25 | 0.4% | 2.00 [47.24, 51.24] | ? |
|                   | Subtotal (95% CI) | 144 | 147 | 223% | 16.78 [14.27, 19.29] | ? |
|                  | Heterogeneity: Tau^2 = 0.00; Chi^2 = 1.17; df = 3 (P = 0.76); I^2 = 0% |  |  |  |  |  |  |  |  |  |
|                  | Test for overall effect: Z = 13.12 (P < 0.0001) |  |  |  |  |  |  |  |  |  |
| 1.16.5 CoQ10 | 19a A. Nadjarzadeh 2012 | 5.78 | 16.88 | 23 | 0.54 | 18.46 | 24 | 5.8% | 5.24 [4.87, 15.35] | ? |
|                   | 24a Mohammad Reza Safarinejad 2012 | 35.8 | 2.7 | 101 | 25 | 2 | 102 | 12.1% | 10.60 [10.15, 11.45] | ? |
|                   | 26a A. Nadjarzadeh 2011 | 5.78 | 16.87 | 23 | 0.51 | 17.29 | 24 | 6.0% | 5.27 [4.50, 15.04] | ? |
|                   | 34a Mohammad Reza Safarinejad 2012 | 5.4 | 2.31 | 98 | 0.8 | 2.39 | 96 | 12.1% | 4.10 [9.94, 5.26] | ? |
|                   | Subtotal (95% CI) | 245 | 360% | 6.91 [1.94, 12.01] | ? |
|                  | Heterogeneity: Tau^2 = 18.09; Chi^2 = 11.98; df = 3 (P < 0.0001); I^2 = 96% |  |  |  |  |  |  |  |  |  |
|                  | Test for overall effect: Z = 2.71 (P = 0.007) |  |  |  |  |  |  |  |  |  |
| 1.16.6 Carnitine | 41a Andrea Iezzi 2004 | 7.94 | 11.66 | 30 | 6.47 | 8.41 | 26 | 9.3% | 1.41 [-0.81, 3.63] | ? |
|                   | Subtotal (95% CI) | 30 | 26 | 9.3% | 1.41 [-0.81, 3.63] | ? |
|                  | Heterogeneity: Not applicable |  |  |  |  |  |  |  |  |  |
|                  | Test for overall effect: Z = 0.65 (P = 0.52) |  |  |  |  |  |  |  |  |  |
| 1.16.7 L-Carnitine | 72a Milat 2015 | 1.63 | 3.16 | 20 | -1.5 | 4.91 | 29 | 11.5% | 3.31 [0.07, 5.53] | ? |
|                   | 74a Markus Lijórac 2016 | 9.2 | 18.2 | 156 | 15.2 | 16.31 | 143 | 10.4% | -8.01 [-19.91, 3.89] | ? |
|                   | Subtotal (95% CI) | 176 | 172 | 22.0% | -4.29 [-10.23, 1.75] | ? |
|                  | Heterogeneity: Tau^2 = 39.02; Chi^2 = 11.69; df = 1 (P < 0.0001); I^2 = 94% |  |  |  |  |  |  |  |  |  |
|                  | Test for overall effect: Z = 0.29 (P = 0.77) |  |  |  |  |  |  |  |  |  |
| 1.16.8 Fish Oil | 80a Tinkl,J. Olsen 2020 | 63.2 | 63.39 | 98 | 62.7 | 175.97 | 125 | 3.6% | 0.50 [14.24, 15.24] | ? |
|                   | Subtotal (95% CI) | 98 | 125 | 3.6% | 0.50 [14.24, 15.24] | ? |
|                  | Heterogeneity: Not applicable |  |  |  |  |  |  |  |  |  |
|                  | Test for overall effect: Z = 0.07 (P = 0.94) |  |  |  |  |  |  |  |  |  |
| 1.16.9 ProEnrich | 23a Martin Imlay 2012 | 16.5 | 18.69 | 132 | 9.5 | 34.3 | 73 | 6.8% | 7.00 [-1.50, 15.50] | ? |
|                   | Subtotal (95% CI) | 132 | 73 | 6.8% | 7.00 [-1.50, 15.50] | ? |
|                  | Heterogeneity: Not applicable |  |  |  |  |  |  |  |  |  |
|                  | Test for overall effect: Z = 1.61 (P = 0.1) |  |  |  |  |  |  |  |  |  |

Total (95% CI) | 825 | 1789 | 100.0% | 6.61 [3.15, 9.86] | ? |

Risk of bias legend:
- A: Random sequence generation (selection bias)
- B: Allocation concealment (selection bias)
- C: Selective reporting (reporting bias)
- D: Other bias
- E: Blinding of participants and personnel (performance bias)
- F: Blinding of outcome assessment detection bias
- G: Incomplete outcome data (attrition bias)
Supplementary Figure 10: Sub-group meta-analysis (intervention based) for sperm morphology (n=29).
**Supplementary Figure 11:** Sub-group meta-analysis (hormone type based) for sperm morphology (n = 12)

| Study or Subgroup | Intervention | Placebo | Mean Difference | Mean Difference | Risk of Bias |
|-------------------|-------------|---------|----------------|----------------|--------------|
| 1.2.7.1 FSH Disc < 200 IU |             |         |                |                |              |
| 22a Nicola Cicaculo 2012 | 13          | 7.11    | 8.1%           | 1.40 [-1.11, 3.93] | ? ? ? ? ? ? ? ? |
| 44a Ettore Croppo 2003 | 52          | 8.03    | 4.7%           | 7.90 [0.50, 16.30] | ? ? ? ? ? ? ? ? |
| 47a Carlo Fuesta 2002 | -07         | 9.72    | 5.5%           | -1.90 [-8.81, 5.03] | ? ? ? ? ? ? ? ? |
| 4/7a Carlo Fuesta 2002 | 54          | 8.58    | 5.8%           | 4.20 [-2.33, 10.73] | ? ? ? ? ? ? ? ? |
| 50a Arminshike 1998  | 02          | 7.06    | 7.6%           | 0.40 [-3.0, 3.32]  | ? ? ? ? ? ? ? ? |
| 67a Yin-man Ding 2015 | 64          | 8.51    | 7.0%           | 4.20 [-0.21, 8.64] | ? ? ? ? ? ? | ? ? ? ? ? ? |
| 67a Yin-man Ding 2015 | -25         | 3.48    | 7.5%           | -4.70 [-8.44, -1.00] | ? ? ? ? ? ? | ? ? ? ? ? ? |
| 67a Yin-man Ding 2015 | 61          | 11.43   | 6.7%           | -3.90 [-1.0, 8.87] | ? ? ? ? ? ? | ? ? ? ? ? ? |
| 76a A. FARRIG 2015    | 6.6         | 8.34    | 7.6%           | 6.36 [2.9, 9.75]   | ? ? ? ? ? ? | ? ? ? ? ? ? |
| 77a R. Selice 2010   | 22          | 7.78    | 8.0%           | 3.50 [0.6, 6.35]   | ? ? ? ? ? ? | ? ? ? ? ? ? |
| Subtotal (95% CI)    | 373         | 306     | 58.5%          | 2.29 [0.0, 4.51]   | ? ? ? ? ? ? | ? ? ? ? ? ? |

Heterogeneity: Tau² = 7.67; Ch² = 26.26, df = 9 (P = 0.032); I² = 66%
Test for overall effect: Z = 2.01 (P = 0.04)

| 1.2.7.2 FSH Disc >= 200 IU |             |         |                |                |              |
| 38a Roberto Paradisi 2006 | 09          | 8.7     | 5.9%           | 2.60 [-3.6, 8.88] | ? ? ? ? ? ? | ? ? ? ? ? ? |
| 67a Yin-man Ding 2015     | 44          | 11.43   | 6.7%           | 2.20 [-2.8, 7.20] | ? ? ? ? ? ? | ? ? ? ? ? ? |
| 78a R. Paradisi 2013      | 02          | 7.45    | 6.7%           | 2.20 [-2.1, 7.75] | ? ? ? ? ? ? | ? ? ? ? ? ? |
| Subtotal (95% CI)         | 100         | 60      | 19.4%          | 2.53 [-0.51, 5.59] | ? ? ? ? ? ? | ? ? ? ? ? ? |

Heterogeneity: Tau² = 0.00; Ch² = 0.03, df = 2 (P = 0.99; I² = 0%)
Test for overall effect: Z = 1.62 (P = 0.11)

| 1.2.7.3 Testosterone      |             |         |                |                |              |
| 25 Push 1918              | 6.16        | 15.49   | 4.8%           | 5.86 [2.48, 14.20] | ? ? ? ? ? ? |
| 45a Davindenbo 2003       | 154         | 12.93   | 7.4%           | 17.40 [13.50, 21.30] | ? ? ? ? ? ? |
| Subtotal (95% CI)         | 135         | 134     | 12.1%          | 12.24 [1.00, 23.49] | ? ? ? ? ? ? |

Heterogeneity: Tau² = 55.54; Ch² = 6.03, df = 1 (P = 0.01; I² = 83%)
Test for overall effect: Z = 2.13 (P = 0.03)

Total (95% CI) 608 500 100.0% 3.68 [0.9, 6.39]

Heterogeneity: Tau² = 22.07; Ch² = 80.44, df = 14 (P < 0.0001); I² = 83%
Test for overall effect: Z = 2.86 (P = 0.008)
Test for subgroup differences: Ch² = 2.90, df = 2 (P = 0.23), I² = 31.1%

**Risk of bias**

- **A** Random sequence generation (selection bias)
- **B** Allocation concealment (selection bias)
- **C** Selective reporting (reporting bias)
- **D** Other bias
- **E** Blinding of participants and personnel (performance bias)
- **F** Blinding of outcome assessment (detection bias)
- **G** Incomplete outcome data (attrition bias)
Supplementary Figure 12: Sub-group meta-analysis (supplement type based) for sperm morphology (n=12)

| Study or Subgroup               | Intervention Mean | Placebo Mean | Mean Difference | Risk of Bias |
|---------------------------------|-------------------|--------------|----------------|--------------|
| 1.25.1 Zinc Sulphate            |                   |              |                | A            |
| 22 Abdul Razzaq 2018            | 12                | 11           | 6.6            | ?            |
| 26 Mahmoud Russein 2012         | 5                 | 12           | -3.7           | ?            |
| 48a Wai Yeong Yong 2002         | -1                | 9.4          | 3.5            | ?            |
| 48a Wai Yeong Yong 2002         | 14.1              | 9.4          | 4.7            | ?            |
| Subtotal (95%CI)                | 144               | 147          | 20.9           | ?            |
| Heterogeneity/Tau²= 0.73; Chi²= 2.61; df= 3 (P < 0.0001); I² = 86% Test for overall effect: Z = 1.25 (P = 0.21) |
| 1.25.2 CoQ10                    |                   |              |                | A            |
| 19a A. Nadjardeghi 2012         | -0.91             | 23           | 4.92           | ?            |
| 24a Mohammad Reza Safarinejad 2012 | 17.6         | 101          | 14.8           | ?            |
| 26a A. Nadjardeghi 2011         | -0.91             | 5.2          | 2.13           | ?            |
| 34a Mohammad Reza Safarinejad 2009 | 2.4              | 2.51         | 9.5            | ?            |
| Subtotal (95%CI)                | 245               | 246          | 39.6           | ?            |
| Heterogeneity/Tau²= 1.42; Chi²= 0.99; df= 3 (P = 0.01); I² = 73% Test for overall effect: Z = 1.73 (P = 0.032) |
| 1.25.3 Carnitine                |                   |              |                | A            |
| 41a Andrea Inf 2004             | 1.28              | 30           | 10.7           | ?            |
| Subtotal (95%CI)                | 30                | 26           | 10.7           | ?            |
| Heterogeneity/Not applicable    |                   |              |                | A            |
| Test for overall effect: Z = 3.94 (P < 0.0001) |
| 1.25.4 L-Carnitine              |                   |              |                | A            |
| 72b Milat 2015                  | 2.01              | 20           | 1.2            | ?            |
| 74a Markou Louvac 2016          | 9.6               | 151          | 7.7            | ?            |
| Subtotal (95%CI)                | 176               | 172          | 10.1           | ?            |
| Heterogeneity/Tau²= 3.19; Chi²= 2.41; df= 1 (P = 0.09); I² = 66% Test for overall effect: Z = 1.34 (P = 0.16) |
| 1.25.5 Fish Oil                 |                   |              |                | A            |
| 80a Tinkold, Jensen 2020        | 7.5               | 98           | 6.6            | ?            |
| Subtotal (95%CI)                | 125               | 125          | 6.6            | ?            |
| Heterogeneity/Not applicable    |                   |              |                | A            |
| Test for overall effect: Z = 0.50 (P = 0.32) |
| 1.25.6 Prostergl                    |                   |              |                | A            |
| 23a Marti inntof 2012           | 11                | 132          | 3.3            | ?            |
| Subtotal (95%CI)                | 132               | 73           | 3.2            | ?            |
| Heterogeneity/Not applicable    |                   |              |                | A            |
| Test for overall effect: Z = 3.95 (P < 0.0001) |
| Total (95%CI)                   | R25               | 789          | 1.0            | ?            |
| Heterogeneity/Tau²= 4.91; Chi²= 113.80; df= 12 (P = 0.00001); I² = 98% Test for overall effect: Z = 2.52 (P = 0.01) Test for subgroup differences: Chi²= 37.36; df= 5 (P < 0.0001); I² = 98.6% |

Risk of bias legend:
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Detection bias (reporting bias)
(D) Other bias
(E) Blinding of participants and personnel (performance bias)
(f) Blinding of outcome assessment (detection bias)
(G) Incomplete outcome data (attrition bias)
Supplementary Figure 13: Overall meta-analysis for total serum testosterone of included RCTs (n=17).

Supplementary Figure 14: Overall meta-analysis for total serum FSH of included RCTs (n=17).
Supplementary Figure 15: Sub-group meta-analysis (intervention based) for total serum testosterone (n = 12).
Supplementary Figure 16: Sub-group meta-analysis (supplement type based) for total serum testosterone (n = 3).

| Study or Subgroup | Intervention Mean | SD | Total | Placebo Mean | SD | Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI | Risk of Bias |
|-------------------|-------------------|----|-------|--------------|----|-------|-----------------------------------|-----------------------------------|--------------|
|                   |                   |    |       |              |    |       |                                   |                                   | A | B | C | D | E | F | G |
| 2.4.2: CoQ10      |                   |    |       |              |    |       |                                   |                                   |   |   |   |   |   |   |   |
| 24a Mohammad Reza Safarinejad 2012 | 19.6 | 4.6 | 101 | 16.7 | 4.4 | 102 | 57.0% | 2.19 (1.86, 4.14) | 5% |
| 24b Mohammad Reza Safarinejad 2019 | 2.8 | 5.5 | 98 | 0.2 | 4.7 | 98 | 22.2% | 2.18 (1.16, 4.04) | 10% |
| Subtotal (95%) | 199 |     |       |              |    |       |                                   |                                   |   |   |   |   |   |   |   |
| Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.76); I² = 0% | | | | | | | | | |
| Test for overall effect: Z = 5.79 (P < 0.0001) | | | | | | | | | |
| 2.4.5: Hid Ch |                   |    |       |              |    |       |                                   |                                   |   |   |   |   |   |   |   |
| 80a Tunkahadesan 2020 | 29.5 | 17.9 | 98 | 21.1 | 164.14 | 1125 | 0.9% | -0.50 (-10.72, 9.72) | 10% |
| Subtotal (95%) | 98 |     |       |              |    |       |                                   |                                   |   |   |   |   |   |   |   |
| Heterogeneity: Not applicable | | | | | | | | | |
| Test for overall effect: Z = 0.10 (P = 0.92) | | | | | | | | | |
| Total (95%) | 297 |     |       |              |    |       |                                   |                                   |   |   |   |   |   |   |   |
| Heterogeneity: Tau² = 0.00; Chi² = 0.48, df = 2 (P = 0.78); I² = 0% | | | | | | | | | |
| Test for overall effect: Z = 5.76 (P < 0.0001) | | | | | | | | | |
| Test for subgroup differences: Chi² = 3.94, df = 1 (P = 0.05), I² = 0% | | | | | | | | | |
| Risk of bias: | | | | | | | | | |
| A (Random sequence generation (selection bias)) | | | | | | | | | |
| B (Allocation concealment (selection bias)) | | | | | | | | | |
| C (Selective reporting (reporting bias)) | | | | | | | | | |
| D (Other bias) | | | | | | | | | |
| E (Blinding of participants and personnel (performance bias)) | | | | | | | | | |
| F (Blinding of outcome assessment (detection bias)) | | | | | | | | | |
| G (Incomplete outcome data (attrition bias)) | | | | | | | | | |

Supplementary Figure 17: Sub-group meta-analysis (SERM type based) for total serum testosterone (n = 3).

| Study or Subgroup | Intervention Mean | SD | Total Mean | Placebo Mean | SD | Total Mean | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI | Risk of Bias |
|-------------------|-------------------|----|------------|--------------|----|------------|-----------------------------------|-----------------------------------|--------------|
|                   |                   |    |            |              |    |            |                                   |                                   | A | B | C | D | E | F | G |
| 2.6.2: Tamoxifen |                   |    |            |              |    |            |                                   |                                   |   |   |   |   |   |   |   |
| 14 Altunkah 1887 | 3.42 | 1.32 | 18 | 1.05 | 16 | 16 | 8.9% | 3.42 (2.59, 5.25) | | |
| 33a Murat 208 | 1.12 | 0.24 | 42 | -0.02 | 0.2 | 25 | 28.7% | 1.15 (0.84, 2.62) | | |
| 33a Murat 208 | 1.07 | 0.22 | 30 | -0.02 | 0.2 | 25 | 28.7% | 1.10 (0.89, 2.11) | | |
| 33a Murat 208 | 1.4 | 0.24 | 31 | -0.02 | 0.2 | 25 | 28.7% | 1.43 (1.31, 1.55) | | |
| 63a A & K, KRA/SE 1992 | 3.32 | 1.32 | 39 | 0.2 | 2 | 37 | 5.1% | 2.70 (1.55, 3.87) | | |
| Subtotal (95%) | 158 | 128 | 100% | 158 | 128 | 100% | 1.50 (1.20, 1.79) | | | |
| Heterogeneity: Tau² = 0.16; Chi² = 51.94, df = 4 (P < 0.0001); I² = 92% | | | | | | | | | |
| Test for overall effect: Z = 9.86 (P < 0.0001) | | | | | | | | | |
| Total (95%) | 158 | 128 | 100% | 158 | 128 | 100% | 1.50 (1.20, 1.79) | | | |
| Heterogeneity: Tau² = 0.16; Chi² = 51.94, df = 4 (P < 0.0001); I² = 92% | | | | | | | | | |
| Test for overall effect: Z = 9.86 (P < 0.0001) | | | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | | | |
| Risk of bias: | | | | | | | | | |
| A (Random sequence generation (selection bias)) | | | | | | | | | |
| B (Allocation concealment (selection bias)) | | | | | | | | | |
| C (Selective reporting (reporting bias)) | | | | | | | | | |
| D (Other bias) | | | | | | | | | |
| E (Blinding of participants and personnel (performance bias)) | | | | | | | | | |
| F (Blinding of outcome assessment (detection bias)) | | | | | | | | | |
| G (Incomplete outcome data (attrition bias)) | | | | | | | | | |
Supplementary Figure 18: Sub-group meta-analysis (intervention based) for total serum FSH (n = 12).

| Study or Subgroup | Intervention Mean | SD | Total Mean | SD | Total Weight | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI | Year | Risk of Bias |
|-------------------|------------------|----|------------|----|--------------|------------------------------------|------------------------------------|------|--------------|
| 2.10.2 Hormones   |                  |    |            |    |              |                                    |                                    |      |              |
| 25 Fuchs 1988     | -0.68            | 1.99 | 23        | 0.43 | 2.15         | 2t 8.3% -1.11 [2.03, -0.13] 1988     |                                    |      |              |
| 51 A. Kamitsuke 1998 | 3.7              | 2.67 | 34        | -0.5 | 3.1          | 3t 6.2% 4.20 [2.9, 5.61] 1998        |                                    |      |              |
| 38a Robert/Paradisi 2006 | 1.7              | 1.67 | 15        | 0.2  | 1.61         | 1t 6.3% 1.90 [0.01, 3.18] 2006       |                                    |      |              |
| 77a R. Selkoe 2010 | 1.6              | 1.91 | 15        | -0.2 | 1.67         | 1t 6.4% 1.40 [0.5, 2.25] 2010        |                                    |      |              |
| 78a H. Paradies 2013 | -0.1             | 1.28 | 45        | 0.2  | 1.67         | 1t 6.4% 0.10 [0.2, 1.02] 2013        |                                    |      |              |
| 5 Helo 2015       | 4.1              | 8.92 | 13        | 3.5  | 42.24        | 1t 0.5% 0.60 [22.29] 24.12 2015      |                                    |      |              |
| Subtotal (95% CI) |                  |    |            |    |              |                                    |                                    | 216  |              |
| Heterogeneity: Tau² = 2.75; Ch² = 43.69, df = 5 (P = 0.00001); P = 98% |
| Test for overall effect: Z = 1.56 (P = 0.11) |

| 2.10.3 Vitamins    |                  |    |            |    |              |                                    |                                    |      |              |
| 80a TimakolUnsen 2020 | 2.8              | 1.99 | 23        | 2.7 | 16.74        | 11t 6.3% 0.10 [-1.5, 1.35] 2020      |                                    |      |              |
| 80a TimakolUnsen 2020 | 2.7              | 7.86 | 20        | 2.7 | 16.74        | 11t 6.2% 0.00 [-1.5, 1.45] 2020      |                                    |      |              |
| 80a TimakolUnsen 2020 | 2.7              | 4.32 | 75        | 2.7 | 16.74        | 11t 6.2% 0.00 [-1.3, 1.38] 2020      |                                    |      |              |
| Subtotal (95% CI)  |                  |    |            |    |              |                                    |                                    | 310  |              |
| Heterogeneity: Tau² = 0.00; Ch² = 0.01, df = 2 (P = 0.99); P = 1% |
| Test for overall effect: Z = 0.10 (P = 0.92) |

| 2.10.4 SERM        |                  |    |            |    |              |                                    |                                    |      |              |
| 14 Alnoklev 1997   | 3.54             | 2.8  | 16        | 0   | 2.28         | 1t 6.1% 3.54 [1.7, 5.31] 1997        |                                    |      |              |
| 63 a R. KRAUS 1992 | 0.5              | 4.49 | 9         | -0.7 | 3.72         | 3t 6.0% 1.20 [0.5, 2.05] 1992        |                                    |      |              |
| 33a Munt 2001      | 6.3              | 4.1  | 4         | 0.3  | 2.67         | 2t 6.1% 6.00 [4.8, 7.26] 2008        |                                    |      |              |
| 33a Munt 2001      | 1.2              | 2.33 | 3         | 0.3  | 2.67         | 2t 6.2% 0.00 [0.3, 2.23] 2008        |                                    |      |              |
| 33a Munt 2001      | 7.1              | 4.66 | 3         | 0.3  | 2.67         | 2t 6.0% 6.80 [4.6, 8.74] 2008        |                                    |      |              |
| Subtotal (95% CI)  |                  |    |            |    |              |                                    |                                    | 158  |              |
| Heterogeneity: Tau² = 6.69; Ch² = 60.69, df = 4 (P = 0.00001); P = 90% |
| Test for overall effect: Z = 3.00 (P = 0.003) |

| 2.10.5 Supplements |                  |    |            |    |              |                                    |                                    |      |              |
| 34a Mohammad-Reza Safarinejad 2019 | -6.4              | 1.8  | 9         | 0.2  | 4.15         | 9t 6.3% -6.20 [-7.3, -5.04] 2009     |                                    |      |              |
| 24a Mohammad-Reza Safarinejad 2012 | 9.6              | 3.6  | 10        | 16   | 4.2          | 10t 6.3% -8.80 [-7.9, -5.72] 2012    |                                    |      |              |
| 80a TimakolUnsen 2020 | 2.4              | 3.95 | 10        | 2.7 | 16.74        | 11t 6.3% -0.20 [-1.5, 0.95] 2020     |                                    |      |              |
| Subtotal (95% CI)  |                  |    |            |    |              |                                    |                                    | 217  |              |
| Heterogeneity: Tau² = 11.65; Ch² = 6844, df = 4 (P < 0.00001); P = 97% |
| Test for overall effect: Z = 2.22 (P = 0.029) |

| Total (95% CI)     |                  |    |            |    |              |                                    |                                    | 971  |              |
| Heterogeneity: Tau² = 11.48; Ch² = 43.91, df = 16 (P < 0.0001); P = 96% |
| Test for overall effect: Z = 0.80 (P = 0.42) |
| Test for subgroup differences: Ch² = 14.98, df = 3 (P = 0.002); P = 79.9% |

Risk of bias rated:
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Selective reporting (reporting bias)
(D) Other bias
(E) Blinding of participants and personnel (performance bias)
(F) Blinding of outcome assessment (detection bias)
(G) Incomplete outcome data (attrition bias)
**Supplementary Figure 19:** Sub-group meta-analysis (SERM type based) for total serum FSH (n = 3).

| Study or Subgroup | Intervention Mean | SD | Total | Mean | SD | Total | Weight | Mean Difference | IV, Random, 95% CI | Risk of Bias |
|-------------------|-------------------|----|-------|------|----|-------|--------|-----------------|-------------------|-------------|
| Tamoxifen         |                   |    |       |      |    |       |        |                 |                   |             |
| 14 Altinkay 1387  | 3.54              | 2.8 | 16    | 2.28 | 16 | 16    | 19.9%  | 3.54 [1.77, 3.13]|                   |             |
| 31a Murat 20B     | 7.1               | 4.56| 30    | 0.26 | 25 | 25    | 19.9%  | 7.10 [4.86, 4.74]|                   |             |
| 33a Murat 20B     | 6.3               | 4   | 42    | 0.26 | 25 | 25    | 20.0%  | 6.30 [4.38, 6.12]|                   |             |
| 33a Murat 20B     | 1.2               | 2.33| 31    | 0.26 | 25 | 25    | 20.0%  | 1.20 [0.43, 2.23]|                   |             |
| 63 a W. Kisuana SE1992 | 0.5           | 4.49| 39    | 0.73 | 37 | 37    | 19.7%  | 0.50 [-0.65, 1.05]|                   |             |
| **Subtotal (95% CI)** | **159**         |    | **128** | **128** | **100.3%** | **3.06** [1.27, 6.05]|                   |             |
| Heterogeneity: Tau = 6.66; Chi² = 40.68, df = 4 (P < 0.0001), P = 90% |
| Test for overall effect Z = 2.00 (P = 0.033) |
| Test for subgroup differences: Not applicable |

**Supplementary Figure 20:** Sub-group meta-analysis (Hormone type based) for total serum FSH (n = 6)

| Study or Subgroup | Intervention Mean | SD | Total | Mean | SD | Total | Weight | Mean Difference | IV, Random, 95% CI | Risk of Bias |
|-------------------|-------------------|----|-------|------|----|-------|--------|-----------------|-------------------|-------------|
| FSH 500 IU        |                   |    |       |      |    |       |        |                 |                   |             |
| 34a Alkamehski 1998 | 17.2              | 2.67| 34    | -1.4 | 31 | 31    | 9.2%   | 18.60 [2.75, 4.61]|                   |             |
| 71a R. Balss 2010 | 16.1              | 1.91| 70    | 1.2  | 21 | 21    | 0.9%   | 17.30 [1.50, 2.25]|                   |             |
| **Subtotal (95% CI)** | **104**          |    | **66** | **66** | **39.5%** | **2.74** [0.64, 4.64]|                   |             |
| Heterogeneity: Tau = 3.57; Chi² = 11.10, df = 1 (P = 0.000099), P = 91% |
| Test for overall effect Z = 1.96 (P = 0.05) |
| Test for subgroup differences: Not applicable |

**FSH 500 IU**

| Study or Subgroup | Intervention Mean | SD | Total | Mean | SD | Total | Weight | Mean Difference | IV, Random, 95% CI | Risk of Bias |
|-------------------|-------------------|----|-------|------|----|-------|--------|-----------------|-------------------|-------------|
| 34a Robertson 2006 | 17                | 1.97| 15    | -1.2 | 16 | 16    | 9.2%   | 18.20 [0.61, 3.19]|                   |             |
| 71a R. Balss 2013 | -0.1              | 1.2 | 45    | 1.67 | 30 | 30    | 0.0%   | -0.10 [0.62, 1.02]|                   |             |
| **Subtotal (95% CI)** | **60**           |    | **30** | **30** | **10.0%** | **0.94** [-0.82, 2.67]|                   |             |
| Heterogeneity: Tau = 1.29; Chi² = 4.98, df = 1 (P = 0.033), P = 90% |
| Test for overall effect Z = 1.05 (P = 0.29) |
| Test for subgroup differences: Not applicable |

**Testosterone**

| Study or Subgroup | Intervention Mean | SD | Total | Mean | SD | Total | Weight | Mean Difference | IV, Random, 95% CI | Risk of Bias |
|-------------------|-------------------|----|-------|------|----|-------|--------|-----------------|-------------------|-------------|
| 25 Pusch 1918     | -0.1              | 1.59| 20    | 0.13 | 21 | 21    | 0.9%   | -0.13 [-0.20, -0.06]|                   |             |
| **Subtotal (95% CI)** | **20**           |    | **20** | **20** | **10.0%** | **0.13** [-0.20, -0.06]|                   |             |
| Heterogeneity: Not applicable |

**Anastrozole**

| Study or Subgroup | Intervention Mean | SD | Total | Mean | SD | Total | Weight | Mean Difference | IV, Random, 95% CI | Risk of Bias |
|-------------------|-------------------|----|-------|------|----|-------|--------|-----------------|-------------------|-------------|
| 5 Helo 2015       | 4.1               | 8.92| 13    | 5.4 | 13 | 13    | 0.4%   | 4.60 [22.22, 24.12]|                   |             |
| **Subtotal (95% CI)** | **206**          |    | **137** | **137** | **10.0%** | **1.24** [0.25, 2.27]|                   |             |
| Heterogeneity: Tau = 2.75; Chi² = 43.50, df = 6 (P = 0.00001), P = 90% |
| Test for overall effect Z = 1.58 (P = 0.01) |
| Test for subgroup differences: Chi² = 9.24, df = 2 (P = 0.03), P = 67.5% |

**Risk of bias**

- Random sequence generation (selection bias)
- Allocation concealment (selection bias)
- Selective reporting (reporting bias)
- Other bias
- Blinding of participants and personnel (performance bias)
- Blinding of outcome assessment (detection bias)
- Incomplete outcome data (attrition bias)
| Section/topic | # | Checklist item                                                                                                                                                                                                                                                                                                                                 | Reported on page # |
|---------------|---|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| TITLE         |   |                                                                                                                                                                                                                                                                                                                                                 | 01               |
| Title         | 1 | Identify the report as a systematic review, meta-analysis, or both.                                                                                                                                                                                                                                                                             | 01               |
| ABSTRACT      |   |                                                                                                                                                                                                                                                                                                                                                 | 03-04            |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 03-04            |
| INTRODUCTION  |   |                                                                                                                                                                                                                                                                                                                                                 | 03-06            |
| Rationale     | 3 | Describe the rationale for the review in the context of what is already known.                                                                                                                                                                                                       | 03-05            |
| Objectives    | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).                                                                                                                                  | 06               |
| METHODS       |   |                                                                                                                                                                                                                                                                                                                                                 | 06-08            |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.                                                                                                                  | 08               |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.                                                                                      | 07               |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.                                                                                                      | 06               |
| Search        | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.                                                                                                                                                           | 06               |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).                                                                                                                                  | 07               |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.                                                                                                                      | 07               |
| Data items    | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.                                                                                                                                               | 07               |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.                                                                                      | 07               |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means).                                                                                                                                                                                                      | 07               |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.                                                                                                                                    | 07               |
## PRISMA 2009 Checklist

| Section/topic                  | #  | Checklist item                                                                                                                                                                                                 | Reported on page # |
|-------------------------------|----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| Risk of bias across studies   | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).                                                                  | 07                |
| Additional analyses           | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.                                                                 | 07                |
| **RESULTS**                   |    |                                                                                                                                                                                                            |                   |
| Study selection               | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.                                                | 08                |
| Study characteristics         | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.                                                                | 08                |
| Risk of bias within studies   | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).                                                                                                | 09                |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.   | 09                |
| Synthesis of results          | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency.                                                                                                       | 09-13             |
| Risk of bias across studies   | 22 | Present results of any assessment of risk of bias across studies (see Item 15).                                                                                                                                  | 09                |
| Additional analysis           | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).                                                                                      | 09-13             |
| **DISCUSSION**                |    |                                                                                                                                                                                                            |                   |
| Summary of evidence           | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).                              | 15-17             |
| Limitations                   | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).                                                 | 17                |
| Conclusions                   | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research.                                                                                         | 17-18             |
| **FUNDING**                   |    |                                                                                                                                                                                                            |                   |
| Funding                       | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.                                                                 | 18                |