# Pharmacologic Interventions in Preventing Ovarian Hyperstimulation Syndrome: A Systematic Review and Network Meta-Analysis
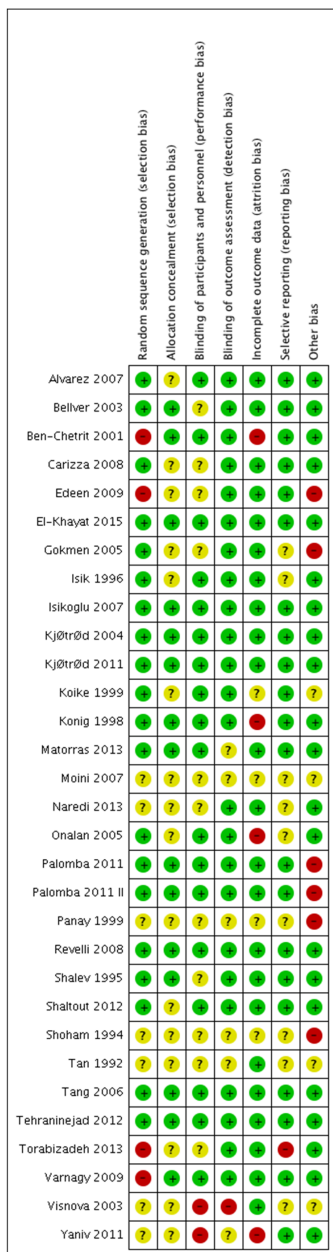
Jun-Liang Guo[1,2,#], Duo-Duo Zhang[1,2,#], Yue Zhao[2,#], Dan Zhang[1], Xi-Meng Zhang[2], Can-Quan Zhou[1,*], Shu-Zhong Yao[1,*]

1 Department of Obstetrics & Gynaecology, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou City, 510080, P.R. China

2 Zhong-shan School of Medicine, Sun Yat-sen University, Guangzhou City, 510082, P.R. China

* Corresponding Author A: Shu-Zhong Yao, M.D., Chief Professor of the Department of Obstetrics & Gynaecology, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou City, 510080. yszsysu@163.com. Correspon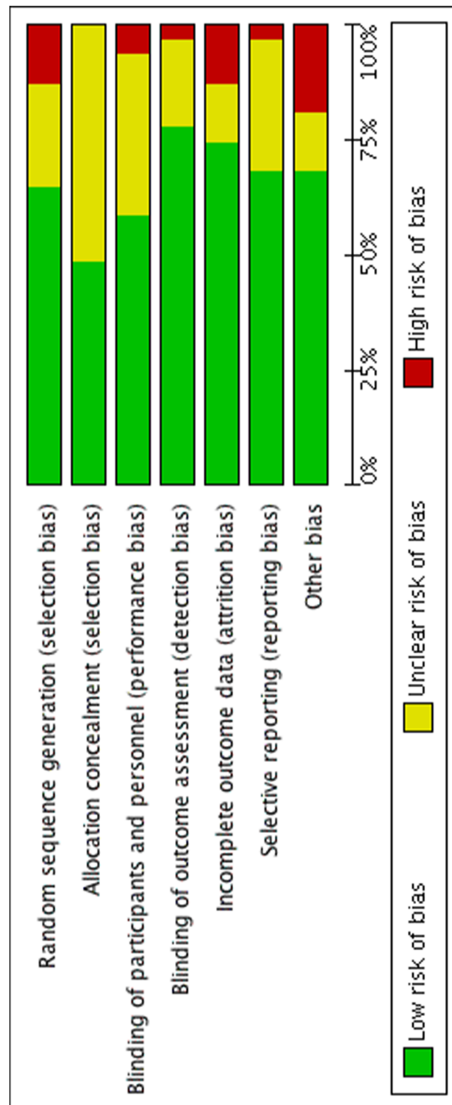ding Author B: Can-Quan Zhou, M.D., Chief Professor of the Centre of Reproductive Medicine, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou City, 510080; zhoucanquan@hotmail.com.

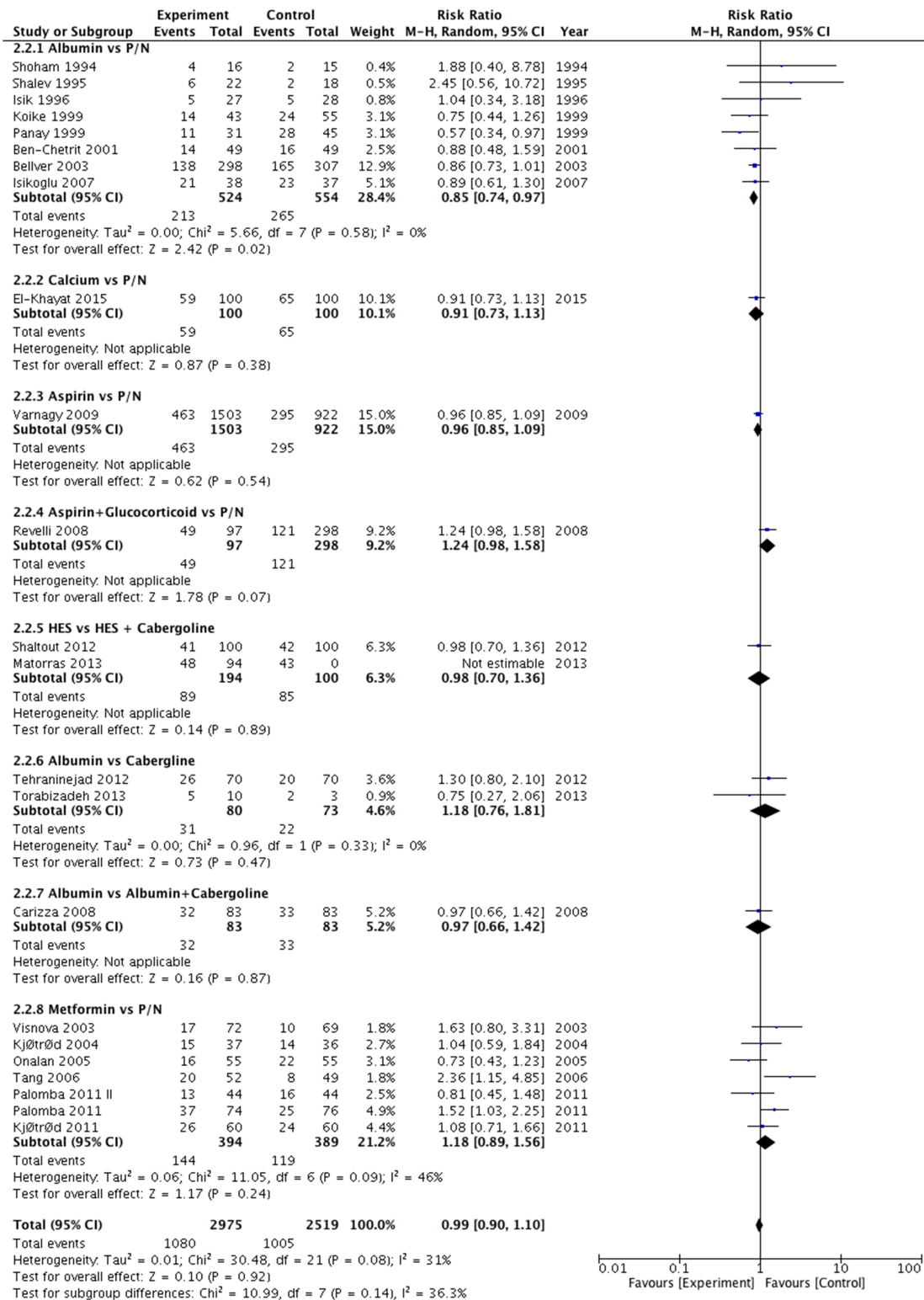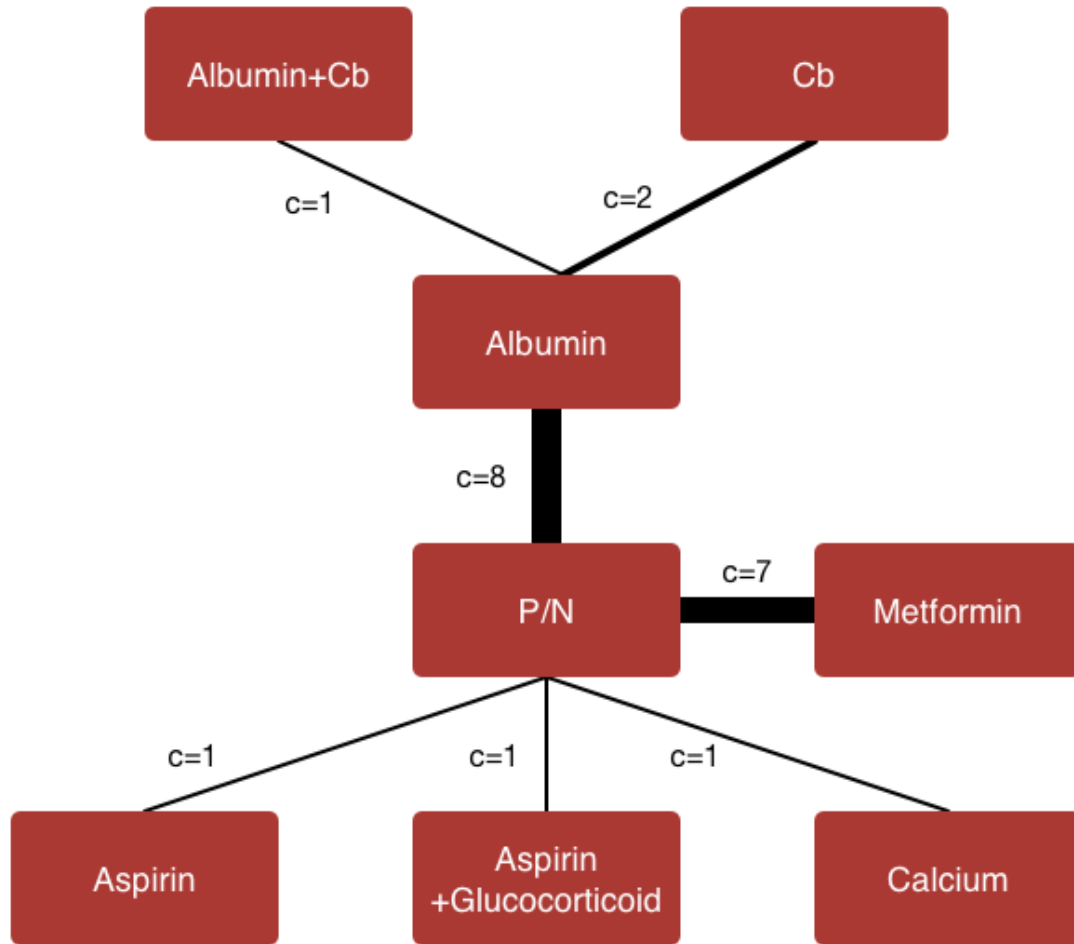# These authors contributed equally to this work.

1                                                      2

**Supplementary Figure A.**
1. Risk of bias summary figure of included studies. 2. Risk of bias figure of included studies.

| Study or Subgroup | Experiment Events | Total | Control Events | Total | Weight | Risk Ratio M-H, Random, 95% CI | Year |
|---|---|---|---|---|---|---|---|
| **2.2.1 Albumin vs P/N** | | | | | | | |
| Shoham 1994 | 4 | 16 | 2 | 15 | 0.4% | 1.88 [0.40, 8.78] | 1994 |
| Shalev 1995 | 6 | 22 | 2 | 18 | 0.5% | 2.45 [0.56, 10.72] | 1995 |
| Isik 1996 | 5 | 27 | 5 | 28 | 0.8% | 1.04 [0.34, 3.18] | 1996 |
| Koike 1999 | 14 | 43 | 24 | 55 | 3.1% | 0.75 [0.44, 1.26] | 1999 |
| Panay 1999 | 11 | 31 | 28 | 45 | 3.1% | 0.57 [0.34, 0.97] | 1999 |
| Ben-Chetrit 2001 | 14 | 49 | 16 | 49 | 2.5% | 0.88 [0.48, 1.59] | 2001 |
| Bellver 2003 | 138 | 298 | 165 | 307 | 12.9% | 0.86 [0.73, 1.01] | 2003 |
| Isikoglu 2007 | 21 | 38 | 23 | 37 | 5.1% | 0.89 [0.61, 1.30] | 2007 |
| **Subtotal (95% CI)** | | 524 | | 554 | 28.4% | 0.85 [0.74, 0.97] | |
| Total events | 213 | | 265 | | | | |

Heterogeneity: Tau² = 0.00; Chi² = 5.66, df = 7 (P = 0.58); I² = 0%
Test for overall effect: Z = 2.42 (P = 0.02)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **2.2.2 Calcium vs P/N** | | | | | | | |
| El-Khayat 2015 | 59 | 100 | 65 | 100 | 10.1% | 0.91 [0.73, 1.13] | 2015 |
| **Subtotal (95% CI)** | | 100 | | 100 | 10.1% | 0.91 [0.73, 1.13] | |
| Total events | 59 | | 65 | | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.87 (P = 0.38)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **2.2.3 Aspirin vs P/N** | | | | | | | |
| Varnagy 2009 | 463 | 1503 | 295 | 922 | 15.0% | 0.96 [0.85, 1.09] | 2009 |
| **Subtotal (95% CI)** | | 1503 | | 922 | 15.0% | 0.96 [0.85, 1.09] | |
| Total events | 463 | | 295 | | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.62 (P = 0.54)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **2.2.4 Aspirin+Glucocorticoid vs P/N** | | | | | | | |
| Revelli 2008 | 49 | 97 | 121 | 298 | 9.2% | 1.24 [0.98, 1.58] | 2008 |
| **Subtotal (95% CI)** | | 97 | | 298 | 9.2% | 1.24 [0.98, 1.58] | |
| Total events | 49 | | 121 | | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 1.78 (P = 0.07)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **2.2.5 HES vs HES + Cabergoline** | | | | | | | |
| Shaltout 2012 | 41 | 100 | 42 | 100 | 6.3% | 0.98 [0.70, 1.36] | 2012 |
| Matorras 2013 | 48 | 94 | 43 | 0 | | Not estimable | 2013 |
| **Subtotal (95% CI)** | | 194 | | 100 | 6.3% | 0.98 [0.70, 1.36] | |
| Total events | 89 | | 85 | | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.14 (P = 0.89)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **2.2.6 Albumin vs Cabergline** | | | | | | | |
| Tehraninejad 2012 | 26 | 70 | 20 | 70 | 3.6% | 1.30 [0.80, 2.10] | 2012 |
| Torabizadeh 2013 | 5 | 10 | 2 | 3 | 0.9% | 0.75 [0.27, 2.06] | 2013 |
| **Subtotal (95% CI)** | | 80 | | 73 | 4.6% | 1.18 [0.76, 1.81] | |
| Total events | 31 | | 22 | | | | |

Heterogeneity: Tau² = 0.00; Chi² = 0.96, df = 1 (P = 0.33); I² = 0%
Test for overall effect: Z = 0.73 (P = 0.47)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **2.2.7 Albumin vs Albumin+Cabergoline** | | | | | | | |
| Carizza 2008 | 32 | 83 | 33 | 83 | 5.2% | 0.97 [0.66, 1.42] | 2008 |
| **Subtotal (95% CI)** | | 83 | | 83 | 5.2% | 0.97 [0.66, 1.42] | |
| Total events | 32 | | 33 | | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.16 (P = 0.87)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **2.2.8 Metformin vs P/N** | | | | | | | |
| Visnova 2003 | 17 | 72 | 10 | 69 | 1.8% | 1.63 [0.80, 3.31] | 2003 |
| KjØtrØd 2004 | 15 | 37 | 14 | 36 | 2.7% | 1.04 [0.59, 1.84] | 2004 |
| Onalan 2005 | 16 | 55 | 22 | 55 | 3.1% | 0.73 [0.43, 1.23] | 2005 |
| Tang 2006 | 20 | 52 | 8 | 49 | 1.8% | 2.36 [1.15, 4.85] | 2006 |
| Palomba 2011 II | 13 | 44 | 16 | 44 | 2.5% | 0.81 [0.45, 1.48] | 2011 |
| Palomba 2011 | 37 | 74 | 25 | 76 | 4.9% | 1.52 [1.03, 2.25] | 2011 |
| KjØtrØd 2011 | 26 | 60 | 24 | 60 | 4.4% | 1.08 [0.71, 1.66] | 2011 |
| **Subtotal (95% CI)** | | 394 | | 389 | 21.2% | 1.18 [0.89, 1.56] | |
| Total events | 144 | | 119 | | | | |

Heterogeneity: Tau² = 0.06; Chi² = 11.05, df = 6 (P = 0.09); I² = 46%
Test for overall effect: Z = 1.17 (P = 0.24)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Total (95% CI)** | | 2975 | | 2519 | 100.0% | 0.99 [0.90, 1.10] | |
| Total events | 1080 | | 1005 | | | | |

Heterogeneity: Tau² = 0.01; Chi² = 30.48, df = 21 (P = 0.08); I² = 31%
Test for overall effect: Z = 0.10 (P = 0.92)
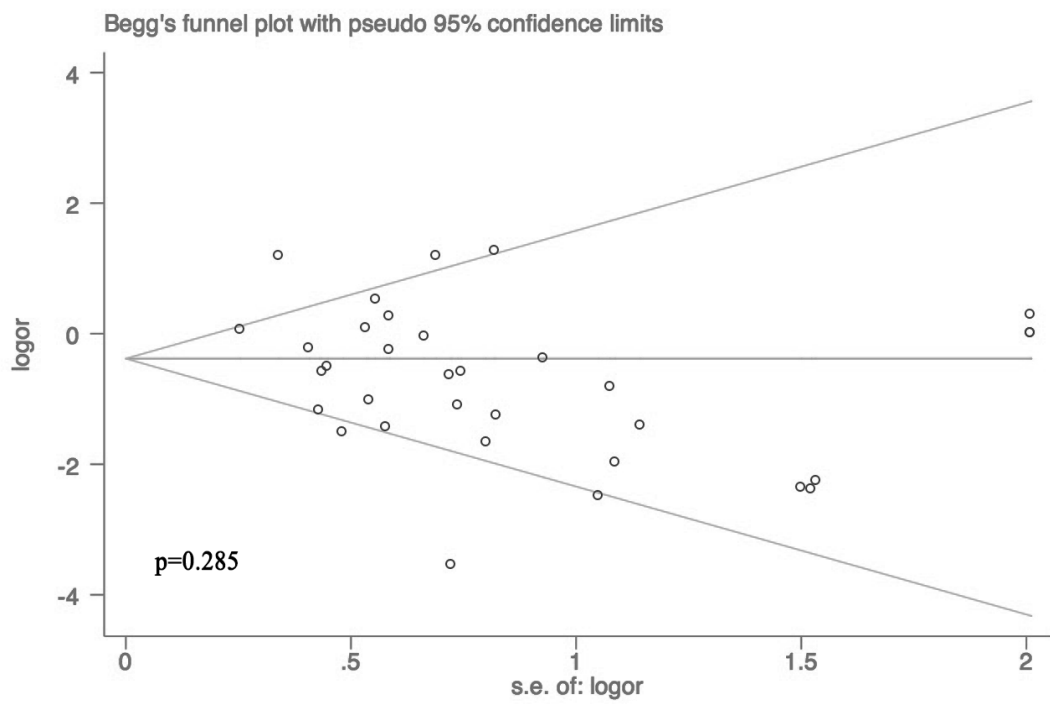Test for subgroup differences: Chi² = 10.99, df = 7 (P = 0.14), I² = 36.3%

**Supplementary Figure B.**

Forest plot of the direct pair-wise head-to-head comparisons between interventions and their comparators for the secondary outcome (pregnancy rate). "Experiment" in the plot represents the intervention, and "control" represents the comparator.

**Supplementary Figure C. Network figure of evidence in the indirect treatment comparison for the secondary outcome (pregnancy rate).** Each red rectangle represents a pharmacological intervention. "c=n" and the thickness of black columns represent the clinical trial number between each comparator.
**Note:** Cb=cabergoline; P/N=placebo or no treatment.

Begg's funnel plot with pseudo 95% confidence limits

**Supplementary Figure D.**
Begg's funnel plot and Begg's regression test *p* value of included studies.

| Study | Intervention Comparator | OHSS incidence | | | | | Pregnancy rate | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Mild OHSS | Moderate-Severe OHSS | Total OHSS | ITT Participant | Actual Participant | Pregnancy | ITT Participant | Actual Participant |
| Tan | Glucocorticoid | NR | NR | 7 | 17 | 17 | NR | NR | NR |
| 1992 | P/N | NR | NR | 6 | 14 | 14 | NR | NR | NR |
| Shoham | ALB | 0 | 0 | 0 | NR | 16 | 4 | NR | 16 |
| 1994 * | P/N | 0 | 4 | 4 | NR | 15 | 2 | NR | 15 |
| Shalev | ALB | 0 | 0 | 0 | 22 | 22 | 6 | 22 | 19 |
| 1995 * | P/N | 0 | 4 | 4 | 18 | 18 | 2 | 18 | 17 |
| Isik | ALB | 0 | 0 | 0 | 27 | 27 | 5 | 27 | 27 |
| 1996 * | P/N | 0 | 5 | 5 | 28 | 28 | 5 | 28 | 28 |
| Konig | HES | NR | 1 | 1 | 53 | 51 | NR | NR | NR |
| 1998 | P/N | NR | 7 | 7 | 51 | 50 | NR | NR | NR |
| Koike | ALB | NR | 13 | 13 | 43 | 43 | 14 | 43 | 43 |
| 1999 * | P/N | NR | 21 | 21 | 55 | 55 | 24 | 55 | 55 |
| Panay | ALB | NR | NR | 0 | NR | 37 | 11 | NR | 31 |
| 1999 * | P/N | NR | NR | 0 | NR | 49 | 28 | NR | 45 |
| Ben-Chetrit | ALB | 36 | 10 | 46 | 49 | 46 | 14 | 49 | 46 |
| 2001 * | P/N | 35 | 6 | 41 | 49 | 41 | 16 | 49 | 41 |
| Visnova | Metformin | NR | NR | 6 | 72 | 72 | 17 | 72 | 72 |
| 2003 * | P/N | NR | NR | 26 | 69 | 69 | 10 | 69 | 69 |
| Bellver | ALB | NR | 34 | 34 | 495 | 488 | 138 | 298 | NR |
| 2003 * | P/N | NR | 32 | 32 | 493 | 488 | 165 | 307 | NR |
| Kjøtrød | Metformin | NR | NR | 1 | 37 | 31 | 15 | 37 | 31 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 2004 * | P/N | NR | NR | 4 | 36 | 32 | 14 | 36 | 32 |
| Gokmen | HES | NR | 8 | 8 | 112 | 112 | NR | NR | NR |
| 2005 * | ALB | NR | 7 | 7 | 105 | 105 | NR | NR | NR |
| | P/N | NR | 24 | 24 | 103 | 103 | NR | NR | NR |
| Onalan | Metformin | 3 | 0 | 3 | 55 | 53 | 16 | 55 | 53 |
| 2005 * | P/N | 4 | 0 | 4 | 55 | 55 | 22 | 55 | 55 |
| Tang | Metformin | NR | 2 | 2 | 52 | 47 | 20 | 52 | 47 |
| 2006 * | P/N | NR | 10 | 10 | 49 | 47 | 8 | 49 | 47 |
| Alvarez | Cabergoline | NR | 11 | 11 | 41 | 35 | NR | NR | NR |
| 2007 | P/N | NR | 20 | 20 | 41 | 32 | NR | NR | NR |
| Isikoglu | ALB | NR | 8 | 8 | 38 | 38 | 21 | 38 | 38 |
| 2007 * | P/N | NR | 6 | 6 | 37 | 37 | 23 | 37 | 37 |
| Moini | Aspirin | NR | NR | 4 | 72 | 72 | NR | NR | NR |
| 2007 | P/N | NR | NR | 17 | 73 | 73 | NR | NR | NR |
| Carizza | Cabergoline +ALB | NR | NR | 9 | 83 | 83 | 33 | 83 | 83 |
| 2008 * | ALB | NR | NR | 15 | 83 | 80 | 32 | 83 | 80 |
| Revelli | Aspirin+ Glucocorticoid | NR | 1 | 1 | 97 | 97 | 49 | 97 | 97 |
| 2008 * | P/N | NR | 7 | 7 | 298 | 298 | 121 | 298 | 298 |
| Varnagy | Aspirin | NR | 2 | 2 | 1503 | 1503 | 463 | 1503 | 1503 |
| 2009 * | P/N | NR | 43 | 43 | 922 | 922 | 295 | 922 | 922 |
| Edeen | Glucocorticoid | NR | NR | 7 | 75 | 75 | NR | NR | NR |
| 2009 | Cabergoline | NR | NR | 2 | 75 | 75 | NR | NR | NR |

| Study | Treatment | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | P/N | NR | NR | 6 | 50 | 50 | NR | NR | NR |
| Yaniv 2011 | Cabergoline | NR | 3 | 3 | 20 | 18 | NR | NR | NR |
| | P/N | NR | 9 | 9 | 20 | 19 | NR | NR | NR |
| Palomba 2011 * | Metformin | 0 | 0 | 0 | 44 | 44 | 13 | 44 | 44 |
| | P/N | 2 | 0 | 2 | 44 | 44 | 16 | 44 | 44 |
| Palomba 2011 II * | Metformin | 3 | 2 | 5 | 60 | 60 | 26 | 60 | 60 |
| | P/N | 11 | 7 | 18 | 60 | 60 | 24 | 60 | 60 |
| Kjøtrød 2011 * | Metformin | NR | 2 | 5 | 74 | 74 | 37 | 74 | 74 |
| | P/N | NR | 3 | 5 | 76 | 75 | 25 | 76 | 75 |
| Shaltout 2012 * | Cabergoline +HES | 5 | 5 | 10 | 100 | 100 | 42 | 100 | 100 |
| | HES | 7 | 14 | 21 | 100 | 100 | 41 | 100 | 100 |
| Tehraninejad 2012 * | ALB | NR | 49 | 49 | 70 | 69 | 26 | 70 | 69 |
| | Cabergoline | NR | 15 | 15 | 70 | 69 | 20 | 70 | 69 |
| Torabizadeh 2013 * | ALB | NR | 10 | 10 | 48 | 48 | 5 | 10 | 10 |
| | Cabergoline | NR | 3 | 3 | 47 | 47 | 2 | 3 | 3 |
| Naredi 2013 | Calcium | 6 | 3 | 9 | 98 | 98 | NR | NR | NR |
| | Cabergoline | 10 | 6 | 16 | 104 | 104 | NR | NR | NR |
| Matorras 2013 * | HES | | NR | 3 | 94 | 94 | 48 | 94 | 94 |
| | Cabergoline +HES | | NR | 5 | 88 | 88 | 43 | 88 | 88 |
| | P/N | NR | 1 | 1 | 33 | 33 | 19 | 33 | 33 |
| El-Khayat | Calcium | 6 | 1 | 7 | 100 | 100 | 59 | 100 | 100 |

| 2015 * | P/N | 11 | 12 | 23 | 100 | 100 | 65 | 100 | 100 |

**Supplementary Table A.** Summary of the extracted data of two outcomes from 31 studies.

**Note:** NR=not reported; P/N=placebo or no treatment.

* Pregnancy rate (secondary outcome) available.

| Intervention | Comparator | Direct Effect | | Indirect Effect | | *p* value |
|---|---|---|---|---|---|---|
| | | LRR | 95%CI | LRR | 95%CI | |
| Albumin | Cabergoline | -1.90 | (-3.30, -0.47) | -0.69 | (-2.01, 0.78) | 0.19 |
| Albumin | HES infusion | -0.17 | (-2.09, 1.95) | -1.94 | (-5.69, 0.81) | 0.28 |
| Albumin | P/N | 0.71 | (-0.02, 1.69) | 0.20 | (-1.44, 1.98) | 0.54 |
| Calcium infusion | Cabergoline | 0.72 | (-1.50, 3.09) | 1.07 | (-1.70, 4.71) | 0.84 |
| Calcium infusion | P/N | 2.99 | (0.40, 6.62) | 2.59 | (0.08, 5.19) | 0.82 |
| Cabergoline | Glucocorticoid | 1.49 | (-0.82, 3.88) | 1.78 | (-0.68, 4.41) | 0.86 |
| Cabergoline | P/N | 1.41 | (0.22, 2.71) | 2.33 | 1.06, 3.76) | 0.27 |

**Supplementary Table B**. Results of the node-splitting analysis for the assessment of inconsistencies. The analysis compares the direct effect with the indirect effect between interventions to estimate inconsistencies in the network analysis. *P* value>0.05 represents no significant difference between the direct and indirect effect.

**Note:** LRR=log relative risk; CI=confidence interval; P/N=placebo or no treatment.

| Drug | Rank 1 | Rank 2 | Rank 3 | Rank 4 | Rank 5 | Rank 6 | Rank 7 | Rank 8 | Rank 9 | Rank 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| ALB | 0 | 0 | 0 | 0 | 1 | 5 | 13 | 29 | 36 | 14 |
| ALB+Cabergoline | 4 | 6 | 7 | 9 | 10 | 12 | 15 | 15 | 9 | 6 |
| Aspirin | 36 | 29 | 15 | 8 | 5 | 3 | 2 | 1 | 0 | 0 |
| Aspirin+Glucocoticoid | 12 | 8 | 7 | 6 | 8 | 8 | 9 | 10 | 9 | 8 |
| Calcium infusion | 35 | 27 | 15 | 9 | 5 | 4 | 2 | 1 | 1 | 0 |
| Cabergoline | 1 | 8 | 22 | 25 | 20 | 13 | 7 | 3 | 0 | 0 |
| Glucocoticoid | 0 | 0 | 1 | 1 | 2 | 4 | 8 | 13 | 17 | 23 |
| HES | 1 | 3 | 7 | 12 | 16 | 20 | 20 | 13 | 6 | 2 |
| HES+Cabergoline | 10 | 13 | 14 | 13 | 13 | 12 | 9 | 6 | 4 | 3 |
| Metformin | 1 | 5 | 11 | 17 | 19 | 19 | 15 | 8 | 3 | 1 |
| P/N | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 13 | 42 |

**Supplementary Table C.** Rank probability result for interventions of the network meta-analysis of the primary outcome (OHSS incidence). The smaller rank number represents the better estimated effect. Each number (expressed in per cent) in this table demonstrates an estimated probability of an intervention to occupy a specific rank.

**Note:** P/N=placebo or no treatment.

| Intervention | Comparator | Relative Risk | 95% CI | *p* value |
|---|---|---|---|---|
| Albumin+Cb | P/N | 0.78 | [0.40,1.53] | 0.473 |
| Cb | P/N | 0.54 | [0.26,1.12] | 0.099 |
| Albumin | Aspirin | 0.79 | [0.58,1.07] | 0.121 |
| Albumin | Aspirin +Glucocorticoid | 0.50 | [0.30,0.84] | 0.009 |
| Albumin | Metformin | 0.56 | [0.38,0.83] | 0.004 |
| Albumin | Calcium infusion | 0.96 | [0.51,1.79] | 0.897 |
| Aspirin | Aspirin +Glucocorticoid | 0.63 | [0.39,1.04] | 0.07 |
| Aspirin | Calcium infusion | 1.22 | [0.67,2.22] | 0.513 |
| Aspirin+ Glucocorticoid | Calcium infusion | 1.93 | [0.92,4.02] | 0.08 |
| Metformin | Aspirin | 1.40 | [0.99,1.99] | 0.057 |
| Metformin | Aspirin +Glucocorticoid | 0.89 | [0.51,1.54] | 0.678 |
| Metformin | Calcium infusion | 1.72 | [0.90,3.28] | 0.102 |

**Supplementary Table D. Results of indirect treatment comparisons (ITCs) based on a generalised linear regression model for the secondary outcome (pregnancy rate).**

**Note**: Cb=cabergoline; CI=confidence interval; P/N=placebo or no treatment.