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# Lowering the Cost of IVF
# A comparison of Conventional and possible cost cutting strategies employed in studies since the year 2000 to 2022: A Systemic Review and Meta-analysis

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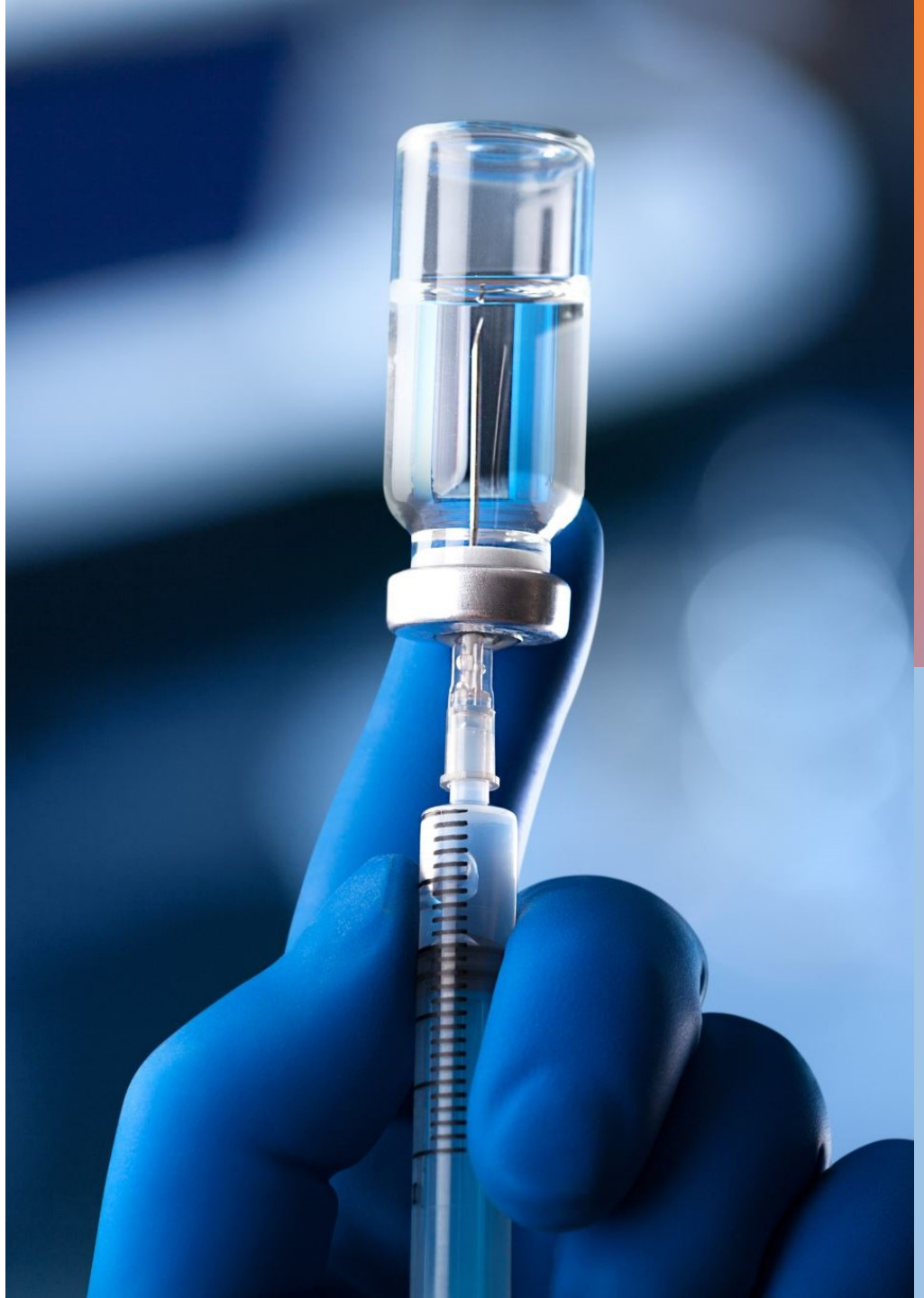
- Conventional IVF is not available in both the public and private sectors of most developing countries
- Where available, it is unaffordable for most couples
- This Systemic Review and Meta-analysis (SRMA) aimed to develop methods for lowering the cost of IVF for adoption in resource-constrained settings.



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# *The cost drivers in conventional IVF include*:

- Infrastructure and equipment
- Investigative procedures (hysterosalpingography(HSG), ultra-sound scan(USS), laparoscope, hormonal assays)
- laboratory infrastructure for embryological procedures
- laboratory equipment ( microscopes, micromanipulators, incubators, etc)
- laboratory consumables (gases, culture medium, etc)
- drugs used in cycle manipulations (gonadotropins, gonadotropin releasing hormone (GnRH) analogues, human chorionic gonadotropin (HCG), etc)
- complications ( ovarian hyper-stimulation syndrome (OHSS), multiple pregnancies, etc).

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# *Strategies to lower cost include*

- simplifying investigations,
- lowering the cost of ovarian stimulation,
- using simple laboratory equipment and procedures,
- using nurse led units, and
- lowering IVF complications

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# Simplifying ovarian stimulation is perhaps the easiest way of reducing IVF costs.

- Ovarian stimulation can be simplified by using
- natural cycle/modified natural cycle IVF(MNC/NC-IVF),
- MS IVF techniques.
- Further decreases can be achieved by
- suppressing premature ovulation with
- non-steroidal anti-inflammatory drugs (NSAIDS)
- low dose clomiphene citrate(CC)
- oral progestins e.g. duphaston

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# *The International Society for Mild Approaches in Assisted Reproduction (ISMAAR)*

| Terminology | Aim | Methodology |
|---|---|---|
| **Natural cycle IVF** | Single oocyte | No medication |
| **Modified Natural cycle IVF** | Single oocyte | HCG only or with GnRH antagonist and Follicle Stimulating Hormone/Human Menopausal Gonadotropin(FSH/HMG) add-back |
| **Mild IVF** | 2–7 oocytes | Low dose FSH/HMG, oral compounds and GnRH antagonist |
| **Conventional IVF** | ≥8 oocytes | GnRH agonist or antagonist conventional FSH/HMG dose |

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# *The Walking Egg project*

- founded in 2010 advocated for affordable and accessible infertility care through
- simplifying investigative procedures,
- IVF laboratory procedures, and
- ovarian stimulation protocols (Ombelet, 2013).

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# *methodology*

- A comprehensive search of studies done since the year 2000 on outcomes of strategies that are deemed to lower the cost of IVF was carried out using MEDLINE, CENTRAL, Cochrane, PUBMED, EMBASE, the Clinical Trials Registry and snowballing from reference lists of selected studies.
- Meta-analysis was done using Review Manager 5.3 software.

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# *Interventions and comparators*

| P | Women Selected for IVF |
|---|---|
| I | Cheaper IVF investigations, Cheaper embryology laboratory techniques, NC-IVF/MNC-IVF/ Mild Stimulation IVF/low Cost IVF, egg sharing, nurse led units |
| C | Conventional IVF/ MNC-IVF/ Mild IVF |
| O | Live birth rate, Pregnancy rate, time to pregnancy |
| T | January 2000 – August 2022 |
| S | Clinical Trials OR Randomised Controlled Trials |

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# Outcome measures

i. Clinical pregnancy rate (CPR)/ cycle in this review was considered as the number of pregnancies obtained from one cycle of IVF confirmed by a serum HCG test and ultrasound presence of a gestational sac by six weeks post embryo transfer.

ii. Ongoing pregnancy rate (OPR)/cycle in this review was defined as the number of pregnancies obtained from one cycle of IVF with evidence of a fetal heart at 12 weeks post embryo transfer.

iii. Live birth rate (LBR)/cycle was defined as babies delivering at a viable gestation who were conceived from one cycle of IVF.

iv. Cumulative CPR/OPR/LBR referred to the total after a defined period or a number of cycles.

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# *Results*

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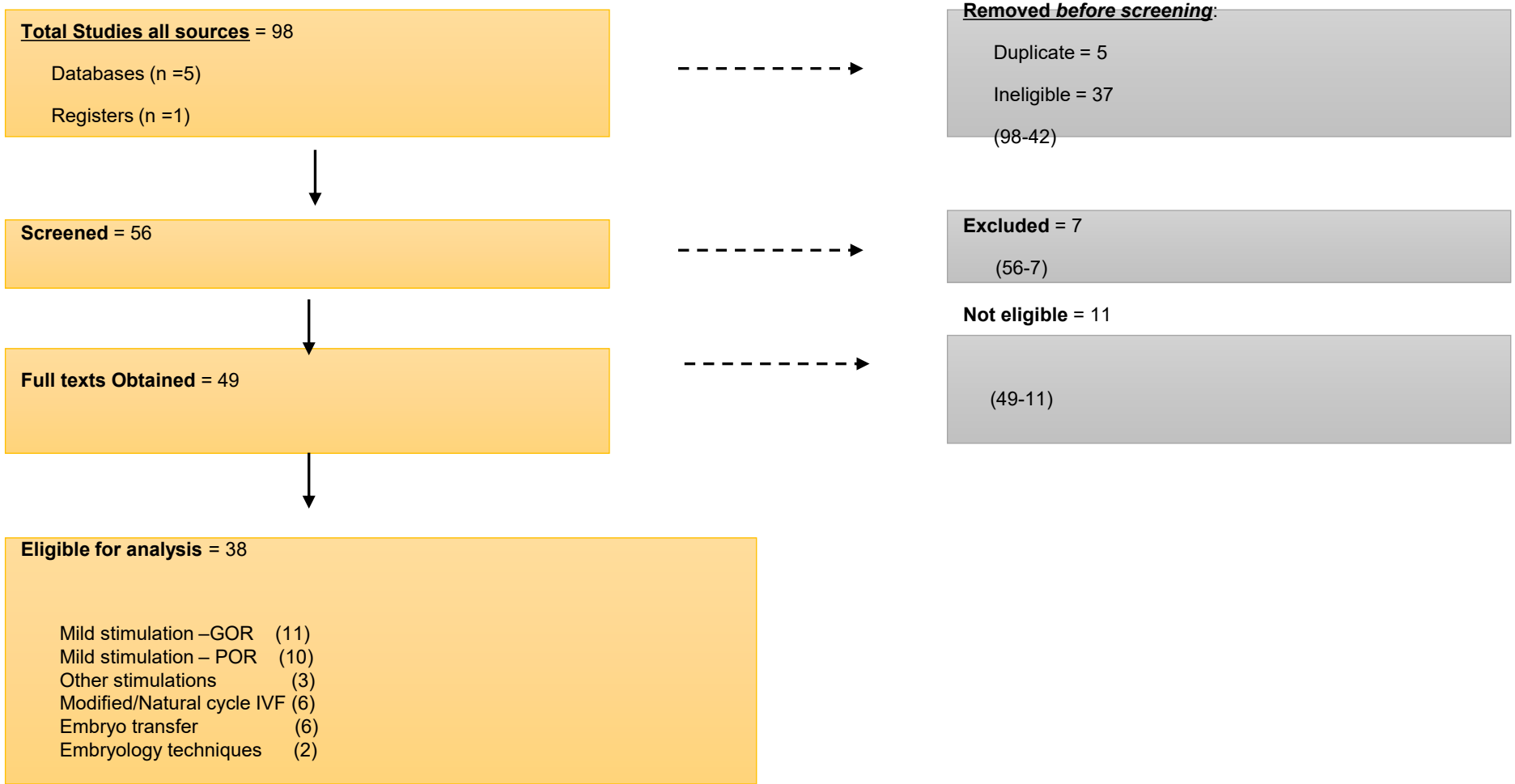
*Figure 1: PRISMA flow diagram*



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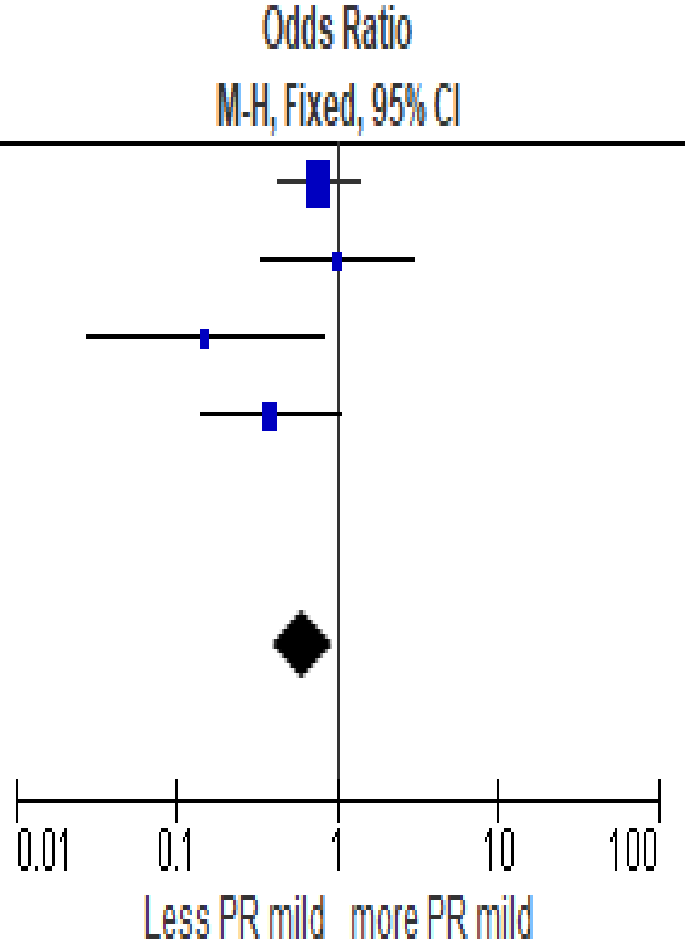
# *Mild versus COH in Good ovarian reserve women CPR/OPR/LBR per cycle*

| Study or Subgroup | mild Events | mild Total | COH Events | COH Total | Weight | Odds Ratio M-H, Fixed, 95% CI | Year |
|---|---|---|---|---|---|---|---|
| (Karimzadeh et al., 2009). | 31 | 100 | 37 | 100 | 48.5% | 0.76 [0.43, 1.38] | 2009 |
| Lou and Huang 2010 | 9 | 30 | 9 | 30 | 12.0% | 1.00 [0.33, 3.02] | 2010 |
| Gleicher, Weghofer and Barad, 2012 | 3 | 14 | 9 | 14 | 13.4% | 0.15 [0.03, 0.81] | 2012 |
| Siristatidis et al., 2017 | 6 | 41 | 22 | 71 | 26.1% | 0.38 [0.14, 1.04] | 2017 |
| Ochin et al., 2018 | 33 | 65 | 6 | 65 | | Not estimable | 2018 |
| **Total (95% CI)** | | **185** | | **215** | **100.0%** | **0.61 [0.40, 0.94]** | |
| Total events | 49 | | 77 | | | | |

Heterogeneity: Chi² = 4.82, df = 3 (P = 0.19); I² = 38%

Test for overall effect: Z = 2.22 (P = 0.03)

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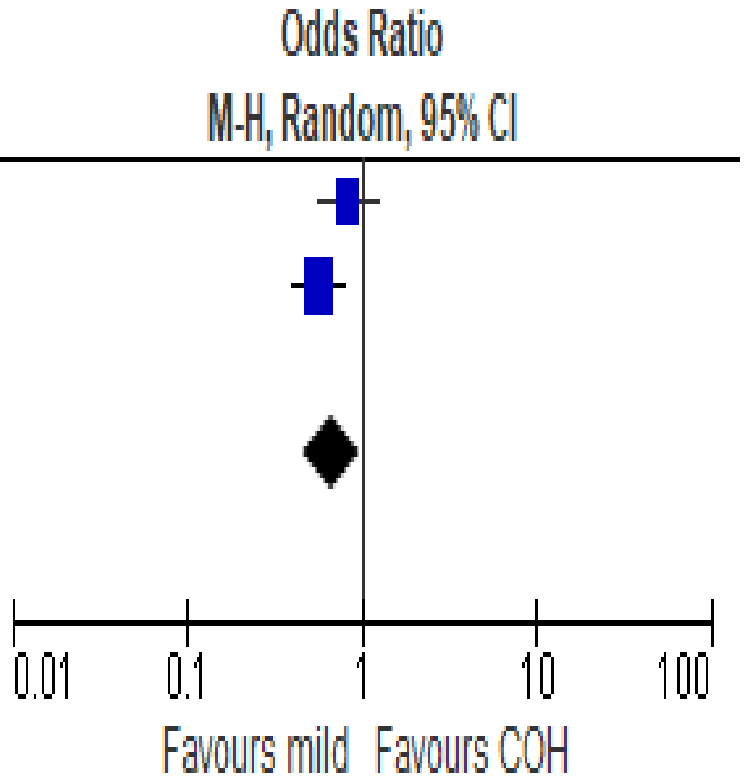
# Mild versus COH in good ovarian reserve women CLBR

| Study or Subgroup | mild Events | mild Total | COH Events | COH Total | Weight | Odds Ratio M-H, Random, 95% CI | Year |
|---|---|---|---|---|---|---|---|
| Heijnen et al., 2007 | 96 | 205 | 102 | 199 | 46.7% | 0.84 [0.57, 1.24] | 2007 |
| Zhang et al., 2016 | 140 | 285 | 176 | 279 | 53.3% | 0.57 [0.40, 0.79] | 2016 |
| Total (95% CI) | | 490 | | 478 | 100.0% | 0.68 [0.46, 1.00] | |
| Total events | 236 | | 278 | | | | |

Heterogeneity: Tau² = 0.04; Chi² = 2.24, df = 1 (P = 0.13); I² = 55%

Test for overall effect: Z = 1.97 (P = 0.05)

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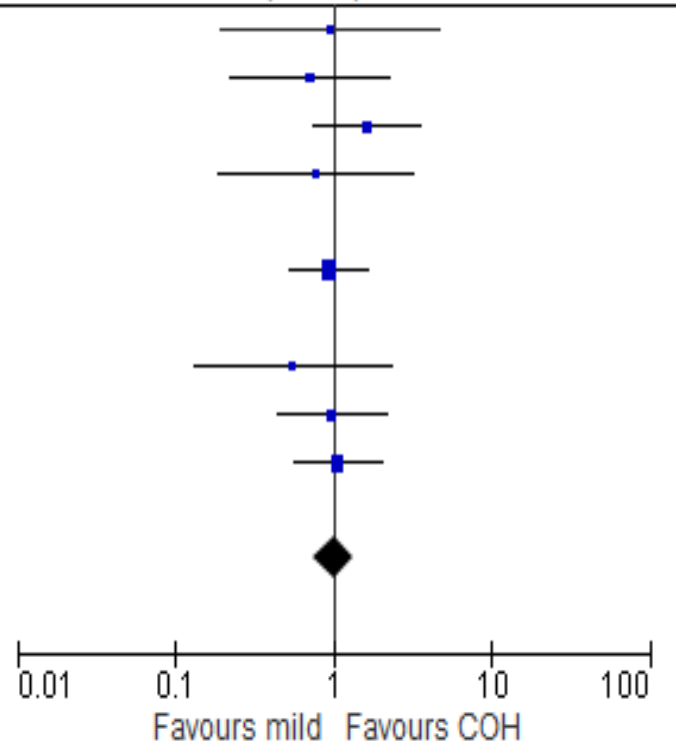
# *Mild versus COH in poor ovarian reserve women*

| Study or Subgroup | mild Events | mild Total | COH Events | COH Total | Weight | Odds Ratio M-H, Fixed, 95% CI | Year |
|---|---|---|---|---|---|---|---|
| Goswami et al., 2004 | 3 | 13 | 6 | 25 | 3.8% | 0.95 [0.20, 4.63] | 2004 |
| Kim et al., 2009 | 6 | 45 | 8 | 45 | 8.4% | 0.71 [0.23, 2.25] | 2009 |
| Karimzadeh et al., 2011 | 19 | 79 | 13 | 80 | 11.9% | 1.63 [0.74, 3.58] | 2011 |
| Mohsen and El Din, 2013 | 4 | 30 | 5 | 30 | 5.2% | 0.77 [0.19, 3.20] | 2013 |
| Revelli et al., 2014 | 47 | 355 | 70 | 30 | | Not estimable | 2014 |
| Youssef et al., 2017 | 25 | 195 | 27 | 199 | 28.2% | 0.94 [0.52, 1.68] | 2017 |
| van Tilborg et al., 2017 | 0 | 0 | 0 | 0 | | Not estimable | 2017 |
| Siristatidis, Salamalekis, et al., 2017 | 4 | 33 | 5 | 25 | 6.1% | 0.55 [0.13, 2.31] | 2017 |
| Yu et al., 2018 | 12 | 35 | 34 | 98 | 14.2% | 0.98 [0.44, 2.21] | 2018 |
| Liu et al., 2020 | 27 | 97 | 25 | 94 | 22.2% | 1.06 [0.56, 2.01] | 2020 |
| **Total (95% CI)** | | **882** | | **626** | **100.0%** | **1.00 [0.74, 1.36]** | |
| Total events | 147 | | 193 | | | | |

Heterogeneity: Chi² = 2.71, df = 7 (P = 0.91); I² = 0%

Test for overall effect: Z = 0.02 (P = 0.98)

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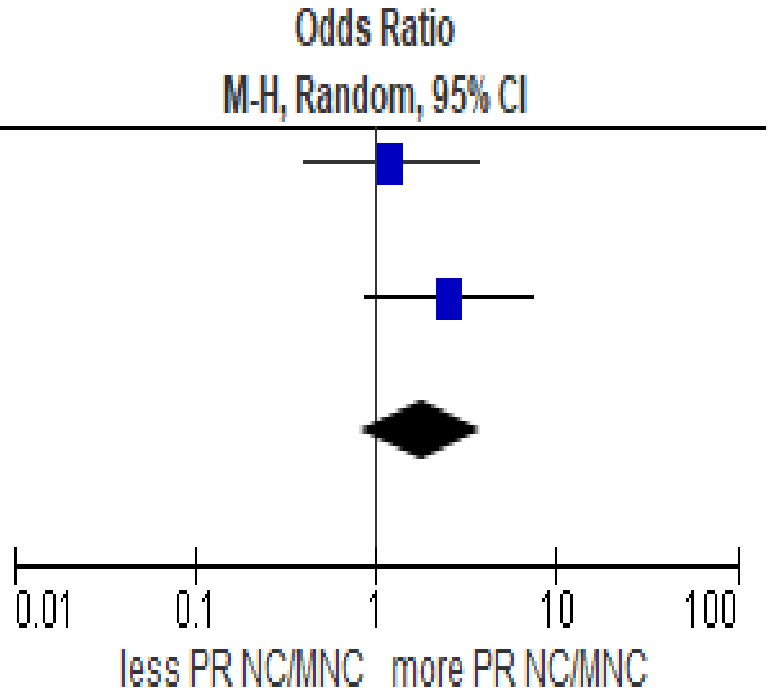
# NC/MNC-IVF versus COH in POR

| Study or Subgroup | NC/MNC Events | NC/MNC Total | COH Events | COH Total | Weight | Odds Ratio M-H, Random, 95% CI | Year |
|---|---|---|---|---|---|---|---|
| Morgia et al., 2004 | 7 | 59 | 7 | 70 | 48.0% | 1.21 [0.40, 3.68] | 2004 |
| Polyzos et al., 2012 | 0 | 0 | 0 | 0 | | Not estimable | 2012 |
| Lainas et al., 2015 | 12 | 161 | 5 | 164 | 52.0% | 2.56 [0.88, 7.44] | 2015 |
| **Total (95% CI)** | | **220** | | **234** | **100.0%** | **1.79 [0.83, 3.86]** | |
| Total events | 19 | | 12 | | | | |

Heterogeneity: Tau² = 0.00; Chi² = 0.91, df = 1 (P = 0.34); I² = 0%

Test for overall effect: Z = 1.48 (P = 0.14)

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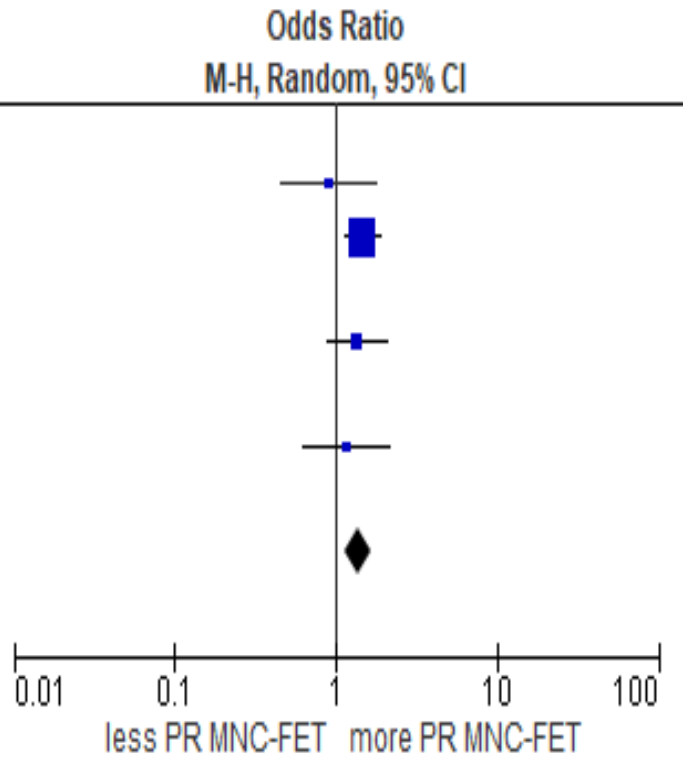
# *NC/MNC-FET was better than Artificial cycle-FET*

| | MNC-FET | | Artificial Cycle - ET | | | Odds Ratio | |
|---|---|---|---|---|---|---|---|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | Year |
| Mounce et al., 2015 | 0 | 0 | 0 | 0 | | Not estimable | 2015 |
| Mounce et al., 2015 | 24 | 72 | 26 | 73 | 7.7% | 0.90 [0.46, 1.79] | 2015 |
| Guan et al., 2016 | 187 | 427 | 276 | 794 | 62.7% | 1.46 [1.15, 1.86] | 2016 |
| Guan et al., 2016 | 0 | 0 | 0 | 0 | | Not estimable | 2016 |
| Groenewoud et al., 2016 | 57 | 495 | 41 | 464 | 20.3% | 1.34 [0.88, 2.05] | 2016 |
| Groenewoud et al., 2016 | 0 | 0 | 0 | 0 | | Not estimable | 2016 |
| Agha-Hosseini et al., 2018 | 33 | 85 | 30 | 85 | 9.3% | 1.16 [0.62, 2.17] | 2018 |
| **Total (95% CI)** | | **1079** | | **1416** | **100.0%** | **1.36 [1.12, 1.64]** | |
| Total events | 301 | | 373 | | | | |

Heterogeneity: Tau² = 0.00; Chi² = 1.96, df = 3 (P = 0.58); I² = 0%

Test for overall effect: Z = 3.13 (P = 0.002)

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## *intravaginal culture (IVC) /simplified culture system (SCS) versus conventional culture*

- The intravaginal culture of oocytes (INVO) system had a live birth rate of 55% compared to 60% for conventional culture ($p>0.5$)
- the simplified culture system (SCS) had ongoing pregnancy rates (OPR) of 30% versus 36.7% for intracytoplasmic sperm injection (ICSI) ($p=0.35$).

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# Discussion

- Equivalent outcomes MS versus cCOH IVF in POR women
- This is in agreement with findings from

- SRMA by Datta *et al.*, 2021 and Song @al 2016 which found no differences in pregnancy rates (CLBR/CPR/OPR) between MS and cCOH in POR.
- the practice committee of the American Society of Reproductive Medicine in their guideline following evidence review did not show a difference in CPR between MS and cCOH protocols in POR women (ASRM, 2018).
- Polyzos and Popovic-Todorovic, 2020 did a SRMA of studies done using MS on POR women and they argued against the universal adoption of MS for all women with POR.

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# *Equivalent CPR in POR who got NC/MNC and cCOH*

- NC/MNC IVF with the low success rate of 6.1 – 13.7% should be offered to those women who cannot afford cCOH or MS or be the main protocol in low resource public centers.
- Pelink who did a retrospective study on such women found a CPR/cycle of 7.9% and CLBR of 44.4% after 9 cycles (Pelinck *et al.*, 2007)

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# NC/MNC-FET was superior to AC-FET

- No studies did a cost effective analysis to see whether the trade-off between CPR and cost savings would justify using NC/MNC-FET if one factors monitoring of the cycle and an HCG trigger which might be used in the later

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# *Debate - low cost versus conventional IVF*

- must be viewed in terms of having some service to offer where no other option exists
- rather than the viewpoint of giving some clients a less efficacious modality of treatment.
- An assumption is made that lowering the entry cost of IVF improves access to those who could not have considered it regardless of the outcomes.
- It is debatable to come up with a pregnancy rate that will justify an intervention and might depend on what odds of success couples deem worthwhile to attempt IVF

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# Conclusion

- Invitro fertilisation can be made cheaper by adopting MS/NC/MNC stimulation protocols for women with POR.
- Women with GOR who cannot afford cCOH protocols should be offered NC, MNC, and MS protocols
- Studies must explore every step in IVF to assess cost-effectiveness to adopt methods with the most minimum cost

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# THANK YOU

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