N-Acetyl Cysteine as an Adjunct to Clomiphene Citrate in Induction of Ovulation

Systematic Review

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IAMANEH Scholarship

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Presentation Outline

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- Objectives
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- Results
- Discussion

Background

Infertility

- Anovulation is estimated to cause 21% of female infertility.
- Group 2 - Hypothalamic pituitary dysfunction or eugonadotrophic, 85% of ovulatory disorders.
- First line treatment for group 2 anovulation should be clomiphene citrate (or tamoxifen) for up to twelve months. *(NICE 2004) .*

Clomiphene Citrate Resistance

- "Failure of ovulation while receiving the 150 mg dose of clomiphene citrate"

  (NICE 2004)

- Highest in PCOS particularly with insulin resistance

- Adjuncts to CC:
  - gonadotropins
  - glucocorticoids (Dexamethasone)
  - insulin sensitizing agents (metformin)
  - bromocryptine
  - aromatase inhibitors

N-Acetyl Cysteine

- A promising agent is N-acetyl-cysteine (NAC), a safe and well-tolerated mucolytic drug.
- Proven activity on insulin secretion in pancreatic cells, acting as an insulin sensitizer.

(De Vries N et al 1993)

- Antiapoptotic activity, protective action against focal ischemia at level of ovary. Apoptosis responsible for follicular atresia. *(De Vries N et al 1993)*
- NAC treatment improves insulin sensitivity, thyroid levels and lipid profile in women with PCO.

(Fulghesu AM et al 2002)

Objectives

Review the effects of NAC in induction of ovulation as an adjunct to CC, in PCO resistant patients, or patients with unexplained infertility.

Methods

- **Search methods for identification of studies**

  - ✓ Different electronic databases including PubMed, Embase, the Reproductive Health Library, the Cochrane Library and Google were searched for randomised controlled trials.
  - ✓ **Keywords**: N Acetylcysteine, Ovulation Induction, Induction of ovulation, Clomiphene, Clomiphene Citrate, Polycystic Ovary Syndrome, Female Infertility.
  - ✓ Different resources of the WHO library and the library of the Faculty of Medicine of the University of Geneva were consulted throughout the preparation of this review.

- **Inclusion criteria:**

✓ Types of studies included

- RCTs comparing CC alone versus CC with NAC in induction of ovulation in PCO patients, or patients with unexplained infertility.

✓ Types of patients studied:

- CC resistant PCOS.
- Unexplained infertility.

✓ Outcome

- Primary outcome: Live birth rate per couple.
- Secondary outcomes: Clinical pregnancy rate, Ovulation rate, Multiple pregnancy per couple, Miscarriage and Incidence of (OHSS).

Results

- The search strategies identified five studies.

- Three studies excluded:
  - not published. *Bedaiwy MA et al 2004*
  - comparing the use of NAC alone versus metformin alone in induction of ovulation. *Elnashar A et al 2007*
  - cross –over trial *Badawy A 2007*

- Two randomised controlled studies with a total of 954 patients:
  - Rizk, A.Y. *et al.* (2005) with 150 participants
  - Badawy A. *et al.*(2006) 804 participants

Characteristics of Studies

- CC 100 mg for 5 days starting on the 2nd or 3rd day of the cycle.

  NAC was 1.2 g/day orally for 5 days with CC in one group, placebo in other.
- Follow up :endometrial thickness, serum E_2 levels, serum progesterone levels(D 21-23).
- hCG was administered when at least one follicle measured ≥18mm.
- Pregnancy was defined as increase in hCG 14 days after hCG injection if menses had not yet occurred.
- *Rizk et al*: PCO.
- *Badawy et al:* unexplained infertility.

Patient Characteristics

	Rizk A.Y. *et al.*		Badawy A *et al.*	
Variable	Study (n=75)	Control (n=75)	Study (n=404)	Control (n=400)
Age (y)	28.9±4.7	28.4±5.7	27.9±4.2	28.1±3.7
Duration of Infertility (years)	5.0±2.9	4.4±2.6	5.1±2.9	4.3±2.7
Weight(kg)	101.3±12.4	99.2±12.3	78.9±6.2	81.3±5.4
Height(m)	164.1±5.31	162.5±5.7	168.0±4.9	161.3±5.1
BMI(*Kg/m^2)	30.5±2.6	30.1±3.1	25.5±3.4	±26.1±3.1

Risk of Bias

Study	Concealed allocation	Randomisation	Blinding	Follow up	ITT	Power calculation	Inclusion bias	Treatment duration
Rizk A.Y. et al 2005	3rd party (nurse) Sealed envelopes	Yes	Double	Yes(according to patient's response)	Yes	Yes	CC resistant patients PCO	1 cycle
Badawy M.A. et al.	Sealed envelopes	Yes	Patients only	Days 10,12 and 14	Yes	Yes	Unexplained infertility	1 cycle

Data Analysis

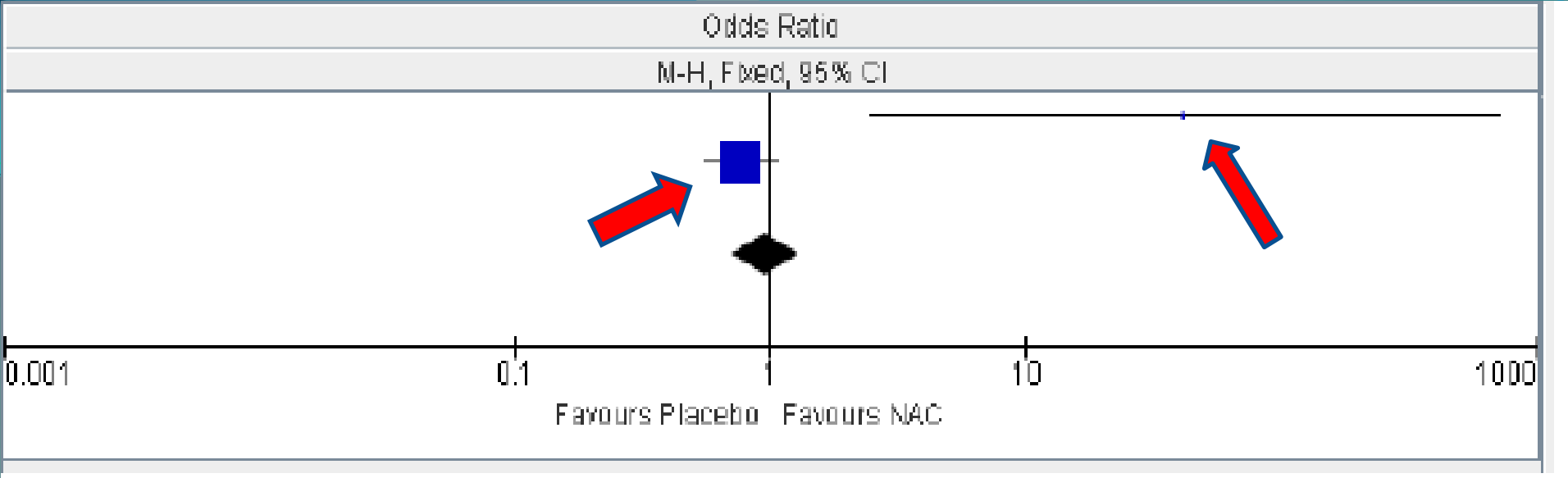
Outcome	Study Group(n=75)	Control Group(n=75)	*P* value
Follicles >18 mm	2.4±0.97	0.01±0.11*	<.001
Ovulation rate	49.3%	1.3%	<.001
Serum E_2 (pg/ml)	360.3±367.9	120±10.0	.007
Serum P (ng/ml)	6.87±5.6	1.8±2.2	<.001
Endometrial thickness	5.9±0.7	4.9±1.9	NS
Pregnancy	16	0	.00006

Rizk et al 2005 NAC versus placebo in PCO

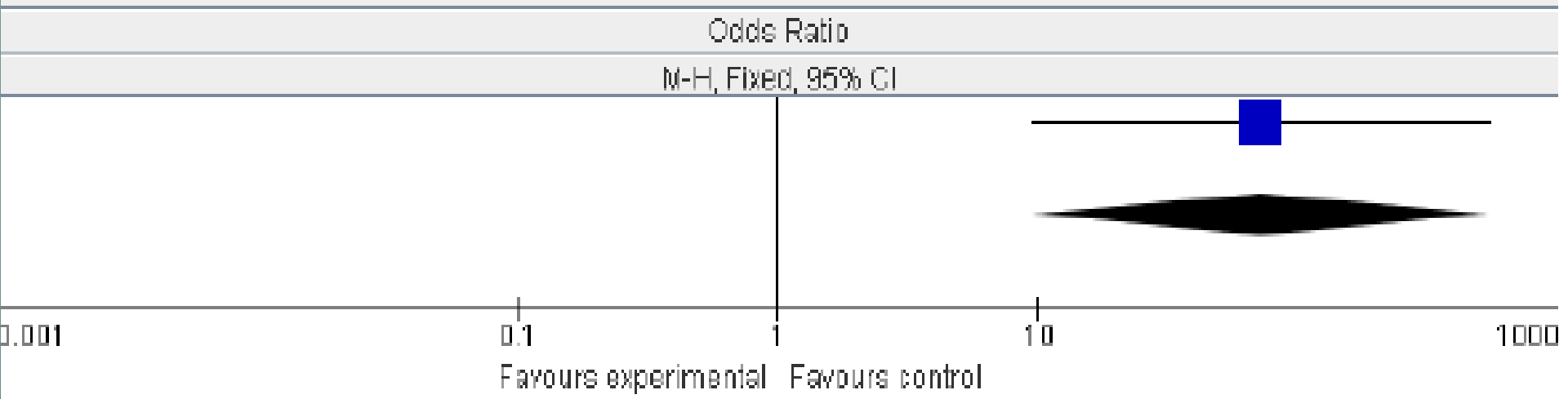
Outcome	Study Group(n=404)	Control(n=400)
No. of follicles >18mm	3.1±0.88	3.2±0.97
Serum E_2 (pg/ml)	398.0±230.4	452.1±290.3
Serum P (ng/ml)	8.3±1.2	8.4±2.3
Endometrial thickness (mm.)	8.3±2.2	8.8±3.1
Pregnancy (%)	90(22.2)	108(27)

Badawy et al 2006 NAC versus placebo in unexplained infertility

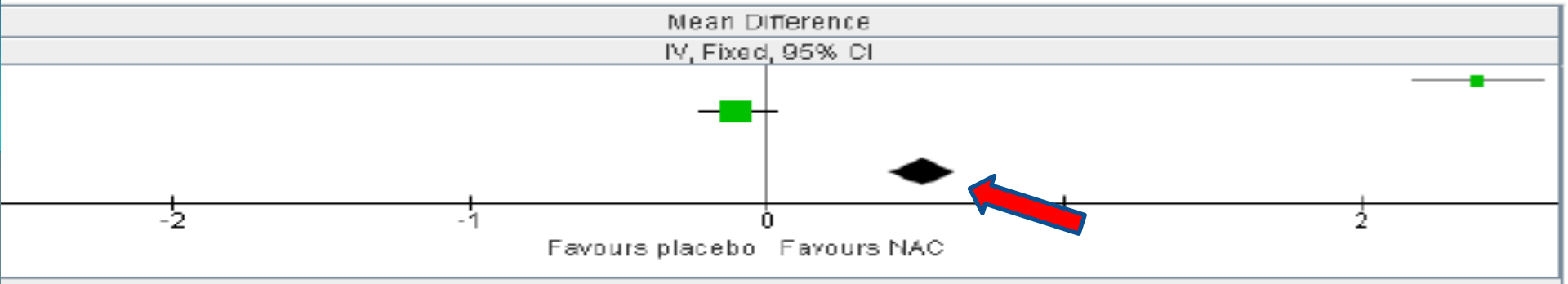
Discussion



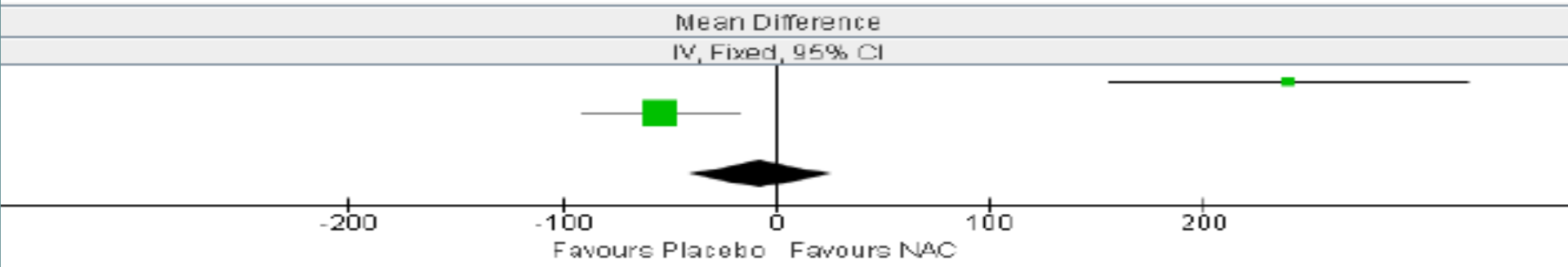
Comparison 1 NAC vs placebo, Outcome Pregnancy rate (per woman)



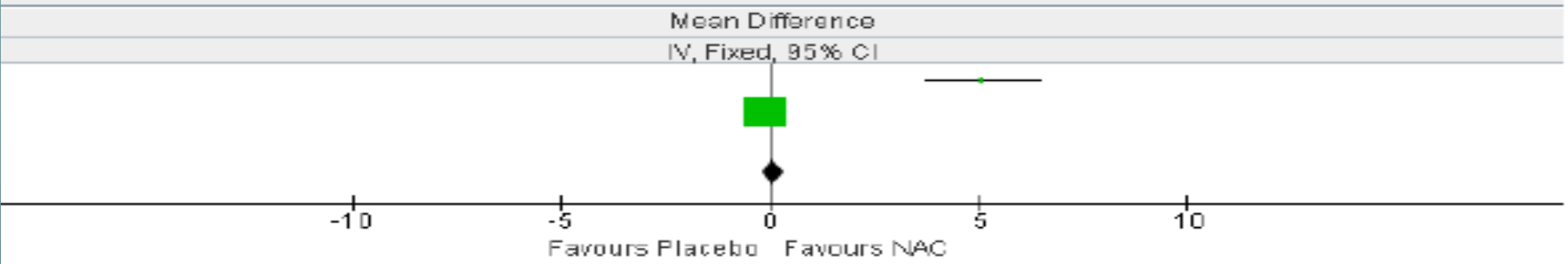
Comparison 1.2 NAC versus placebo, Outcome 2 Ovulation rate (per woman)



Comparison 1.3 NAC versus placebo, Outcome 3 Number of follicles >18 mm



Comparison 1.4 NAC versus placebo. Outcome 4 E_2 levels



Comparison 1.5 NAC versus placebo, Outcome 5 Progesterone levels

- NAC shows promising effect in PCO patients due to its metabolic actions especially insulin sensitising effect.
- Lack of effect in patients with unexplained infertility can be explained by absence of insulin resistance .
- Larger doses may be needed for other actions of NAC to exert a positive effect.
- However, in both studies, there was a statistically significant value in increasing number of follicles.

THE DEBATE CONTINUES.

Tim Kreider *The Pain -- When Will It End?* http://www.thepaincomics.com

Conclusion

- This review could not find strong evidence in favor of NAC as an adjunct to CC.
- Further studies are needed
- Studies must be
  - properly designed (CONSORT) statement
  - include more patients
  - run for at least 12 treatment cycles

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Thank You!

Questions