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

Systematic Review

Training Course in Sexual and Reproductive Health Research
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IAMANEH Scholarship

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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. \textit{Bedaiwy MA et al 2004}
- comparing the use of NAC alone versus metformin alone in induction of ovulation. \textit{Elnashar A et al 2007}
- cross-over trial \textit{Badawy A 2007}

Two randomised controlled studies with a total of 954 patients:

- Rizk, A.Y. \textit{et al.} (2005) with 150 participants
- Badawy A. \textit{et al.}(2006) 804 participants
Characteristics of Studies

- CC 100 mg for 5 days starting on the 2\textsuperscript{nd} or 3\textsuperscript{rd} 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 $\geq 18$ mm.
- Pregnancy was defined as increase in hCG 14 days after hCG injection if menses had not yet occurred.
- \textit{Rizk et al}: PCO.
- \textit{Badawy et al}: unexplained infertility.
## Patient Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rizk A.Y. et al.</th>
<th>Control (n=75)</th>
<th>Badawy A et al.</th>
<th>Study (n=404)</th>
<th>Control (n=400)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>28.9±4.7</td>
<td>28.4±5.7</td>
<td>27.9±4.2</td>
<td>28.1±3.7</td>
<td></td>
</tr>
<tr>
<td>Duration of Infertility (years)</td>
<td>5.0±2.9</td>
<td>4.4±2.6</td>
<td>5.1±2.9</td>
<td>4.3±2.7</td>
<td></td>
</tr>
<tr>
<td>Weight(kg)</td>
<td>101.3±12.4</td>
<td>99.2±12.3</td>
<td>78.9±6.2</td>
<td>81.3±5.4</td>
<td></td>
</tr>
<tr>
<td>Height(m)</td>
<td>164.1±5.31</td>
<td>162.5±5.7</td>
<td>168.0±4.9</td>
<td>161.3±5.1</td>
<td></td>
</tr>
<tr>
<td>BMI(*Kg/m²)</td>
<td>30.5±2.6</td>
<td>30.1±3.1</td>
<td>25.5±3.4</td>
<td>±26.1±3.1</td>
<td></td>
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</tbody>
</table>
## Risk of Bias

<table>
<thead>
<tr>
<th>Study</th>
<th>Concealed allocation</th>
<th>Randomisation</th>
<th>Blinding</th>
<th>Follow up</th>
<th>ITT</th>
<th>Power calculation</th>
<th>Inclusion bias</th>
<th>Treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rzik A.Y. et al 2005</td>
<td>3rd party (nurse)</td>
<td>Yes</td>
<td>Double</td>
<td>Yes(according to patient’s response)</td>
<td>Yes</td>
<td>Yes</td>
<td>CC resistant</td>
<td>1 cycle patients PCO</td>
</tr>
<tr>
<td></td>
<td>Sealed envelopes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Badawy M.A. et al</td>
<td>Sealed envelopes</td>
<td>Yes</td>
<td>Patients only</td>
<td>Days 10,12</td>
<td>Yes</td>
<td>Yes</td>
<td>Unexplained</td>
<td>1 cycle infertility</td>
</tr>
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</tbody>
</table>
Data Analysis
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Group (n=75)</th>
<th>Control Group (n=75)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follicles &gt;18 mm</td>
<td>2.4±0.97</td>
<td>0.01±0.11*</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Ovulation rate</td>
<td>49.3%</td>
<td>1.3%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Serum E₂ (pg/ml)</td>
<td>360.3±367.9</td>
<td>120±10.0</td>
<td>.007</td>
</tr>
<tr>
<td>Serum P (ng/ml)</td>
<td>6.87±5.6</td>
<td>1.8±2.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Endometrial thickness</td>
<td>5.9±0.7</td>
<td>4.9±1.9</td>
<td>NS</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>16</td>
<td>0</td>
<td>.00006</td>
</tr>
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</table>

Rizk et al 2005 NAC versus placebo in PCO
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Group (n=404)</th>
<th>Control (n=400)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of follicles &gt;18mm</td>
<td>3.1±0.88</td>
<td>3.2±0.97</td>
</tr>
<tr>
<td>Serum $E_2$ (pg/ml)</td>
<td>398.0±230.4</td>
<td>452.1±290.3</td>
</tr>
<tr>
<td>Serum P (ng/ml)</td>
<td>8.3±1.2</td>
<td>8.4±2.3</td>
</tr>
<tr>
<td>Endometrial thickness (mm)</td>
<td>8.3±2.2</td>
<td>8.8±3.1</td>
</tr>
<tr>
<td>Pregnancy (%)</td>
<td>90 (22.2)</td>
<td>108 (27)</td>
</tr>
</tbody>
</table>

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 E₂ 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.
...it is not "just" a theory. It is a theory that elegantly explains all the available data. Is overwhelmingly supported by epipircoööönäh...
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
I wish to thank Dr. Regina Kulier for her guidance and support. Thanks also to Dr. Thomas Allen for his help with the research.

Finally, thanks to GFMER and WHO for arranging the research methodology course, and IAMANEH for the scholarship that made it possible to attend this course.
Questions