

NAC: A Powerful Antioxidant and Anti-inflammatory in Reproductive Health:

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Abstract:

Oxidative stress and inflammation are known to be involved in the development of different female reproductive disorders, including polycystic ovary syndrome, endometriosis, subfertility/infertility, and pregnancy wastage. Excess ROS, mitochondrial dysfunction, and inflammation signaling can affect follicular development, quality of oocytes, receptivity of endometrium, implantation, and embryonic development. N-acetyl cysteine (NAC), a derivative of cysteine and a GSH precursor, has attracted interest because of its antioxidant, anti-inflammatory, and cytoprotective effects. The main aim is to assess the pharmacological actions of NAC and evidence of potential therapeutic benefit for female reproductive health, including PCOS, endometriosis, and assisted reproductive technologies (IVF/ICSI). All accessible experimental clinical RCT, SR, and meta-analytic data on NAC and female reproductive diseases were considered. The focus was on the effects of NAC on glutathione, ROS scavenging, the Nrf2 pathway, NF- κ B inflammation mitochondria, and reproductive term effects.

Results: (1) PCOS: for ovulation and pregnancy, research suggested improvements, while a recent meta-analysis showed a trend towards benefit for progesterone and endometrial thickness.

(2) Endometriosis: preliminary clinical evidence suggested notable impact on pelvic pain, analgesic requirements, and reductions in endometriosis size, but high study variability prevented aggregation in a meta-analysis.

(3) IVF/ICSI, in which clinical pregnancy and live-birth datasets showed mixed effects.

At last concluding that N-Acetyl cysteine appears to be a promising adjunctive antioxidant and anti-inflammatory treatment for female reproductive health. Though, it should not be regarded as a treatment for infertile women suffering from PCOS, endometriosis, or infertility per se. Well-powered, standardized randomized controlled trials are needed to determine the optimal dose and duration of treatment, patient selection, long-term safety, and effect on pregnancy outcome, particularly live birth.

Keywords: N-acetylcysteine; oxidative stress; antioxidant; anti-inflammatory; glutathione; reactive oxygen species; polycystic ovary syndrome; endometriosis; infertility; assisted reproductive technology; IVF/ICSI.

1. Introduction:

Oxidative stress and chronic inflammation are two biological processes that are tightly linked and highly contribute to the development and worsening of various acute and chronic diseases [1, 2]. When this balance is upset, oxidative stress results that lead to cell damage through various mechanisms like lipid

peroxidation, protein oxidation, DNA damage, and mitochondrial dysfunction [2, 3]. At the same time, chronic inflammatory responses can contribute to tissue damage by inducing the production of pro-inflammatory cytokines, chemokines, and other inflammatory mediators. Ultimately, this will result in further progression of the disease. Antioxidants are a heterogeneous group of chemical compounds that can chemically interact with reactive oxygen and nitrogen species and, in this way, protect cells from oxidative damages and allow them to continue performing their normal functions. Such agents can be internally produced by our body, such as glutathione, superoxide dismutase, catalase, and glutathione peroxidase, or externally obtained, like vitamins, polyphenols, flavonoids, and pharmacological antioxidants [2, 4]. In contrast, anti-inflammatory agents work to diminish inflammation by altering immune responses, blocking inflammatory signaling pathways, and reducing the production of inflammatory mediators. Growing research indicates that many therapeutic drugs have the combination of antioxidant and anti-inflammatory properties, this way helping in a synergistic manner to protect the body from oxidative and inflammatory damages. Pathophysiological involvement of the oxidative stress-inflammation axis has been found for most human diseases. Numerous conditions like cardiovascular diseases, neurodegenerative diseases, diabetes mellitus, cancer, chronic kidney disease, respiratory diseases, autoimmune diseases, and reproductive disorders can be identified as oxidative stress-inflammation-related diseases [3, 5, 6]. In line with current understanding, the tradition of combining in a single formulation the different compounds that target separately oxidative stress and inflammatory pathways is abandoned in favor of coupling diverse activities in a single molecular entity. The latter approach works as a source of novel therapeutic leads and inspirations for drug development, offering the possibility of higher efficacy and better safety. Modern biomedical research continues to unveil the potentials of both natural and synthetic compounds possessing dual antioxidant and anti-inflammatory properties as a means for clinical improvement. Understanding completely the molecular bases of these protective effects is very important in devising therapeutic strategies intended for the treatment. This article aims to cover the topics related to oxidative stress and inflammation from the biological perspective, the modus operandi of antioxidant and anti-inflammatory substances, and their therapeutics, as well as recent discoveries backing their usage in the prevention and treatment of diseases. Reproductive health is a fundamental aspect of wellness and is shaped by many factors, including genetics, hormones, environment, and lifestyle. Studies reveal that oxidative stress and chronic inflammation are the main perpetrators behind the development of various reproductive disorders in women and men [7–9]. Generation of excessive levels of reactive oxygen species (ROS) and weak antioxidant defense systems lead to disturbance of cell homeostasis, resulting in membrane degradation, protein damage, DNA breakage, mitochondrial malfunction, and cell death [7, 8]. At the same time, continuous inflammatory reactions, which are marked by high levels of pro-inflammatory cytokines and other inflammatory mediators, worsen reproductive capacity by degrading gamete quality, disrupting hormone balance, reducing implantation, and affecting embryonic development [8, 10]. These pathways have been linked to disorders like polycystic ovary syndrome (PCOS), endometriosis, unexplained infertility, recurrent miscarriages, diminished ovarian reserve, male infertility, and reproductive problems related to metabolic disorders [9, 11–13]. NAC, shorthand for N-acetylcysteine, is a sulfur-containing compound derived from the amino acid L-cysteine, which has drawn a lot of interest mainly because of its strong antioxidant and anti-inflammatory effects. Initially, it was found to be used as a mucolytic and for the treatment of paracetamol overdoses [14, 15]. Though NAC continues to gain popularity as a therapeutic agent in various medical scenarios. The major way through which it works is by restoring the levels of glutathione

inside the cells—an antioxidant that is very critical to the human body [16, 17]. By this means, cells' protective systems get strengthened against harmful effects of oxidative stress. Also, NAC directly eliminates the reactive oxygen and nitrogen species, helps in maintaining mitochondrial health, influences redox-sensitive signaling pathways, and dulls inflammatory responses via suppression of pro-inflammatory cytokines and transcription factors like nuclear factor-kappa B (NF- κ B) [18, 19]. Consequent to the discovery of diverse pharmacological actions of NAC, there has been a surge in its utilization and interest in reproductive medicine. As a result of clinical and experimental research, NAC has favorable effects on several reproductive indices: it restores menstrual cycles, improves egg and sperm quality, protects from oxidative and inflammatory damages, enhances insulin action in PCOS, elevates endometrial receptivity, and makes conception easier, leading to a successful pregnancy outcome [20–24]. In addition, given its excellent safety margin, low cost, and wide accessibility, NAC stands out as a potential therapeutic agent that can be conveniently used with other treatments for reproductive disorders [25, 26]. But much more remains to be explored about the exact molecular pathways involved, proper doses to be given, long-term safety, and overall effectiveness of NAC in different reproductive disorders via rigorous scientific studies. The aim of this article is to describe the antioxidant and anti-inflammatory actions of NAC, to review the available data on the effects of NAC on the reproductive health of both sexes, and to discuss the therapeutic prospects, clinical applications, limitations, and opportunities for further research in reproductive medicine.

2. NAC: Chemistry and pharmacology:

2.1 Chemistry of N-Acetyl Cysteine

N-Acetyl cysteine (NAC) is an N-acetyl derivative of the non-essential amino acid L-cysteine, which is obtained naturally [19, 27]. Acetylation of the amino group increases the chemical stability of the compound and its oral bioavailability while leaving the reactive sulfhydryl (-SH) group intact, which is responsible for many of its pharmacological effects [28, 29]. Due to its distinctive chemical properties, NAC can act as both a direct antioxidant and a glutathione precursor, and this forms the basis of its use as a therapeutic agent.

And NAC is also a precursor of glutathione, the important intracellular free radical scavenger, as well as the limiting amino acid in its biosynthesis [30–32]. Increased glutathione synthesis in the cells also can protect tissues from oxidative injury. And these chemical properties of NAC account for its famous bucolic property, in which the disulphide bonds of the glycoproteins are reduced and inspissated mucus is liquefied [33,34]. NAC exhibits high water solubility and, for this reason, is generally manufactured in forms such as tablets or effervescent tablets for oral administration, capsules, inhalation solutions, and intravenous preparation [25, 35].

Once administered, NAC is acetylated to L-cysteine; this then feeds glutathione pathways and other sulfur pathways [36–38]. It is chemically stable when stored appropriately but is prone to oxidation, becoming a disulphide if left in air for long periods of time [19].

The distinctive chemical structure of NAC, particularly its thiol function group as well as its ability to restore the endogenous levels of glutathione, gives pharmacological rationale for its antioxidant, anti-inflammatory, cytoprotective, and immune-modulating activity. Based on this, NAC has been extensively researched and used in several conditions, including respiratory diseases, acetaminophen toxicity, cardiovascular and neurodegenerative disorders, cancer, and reproductive medicine [25, 27, 39].

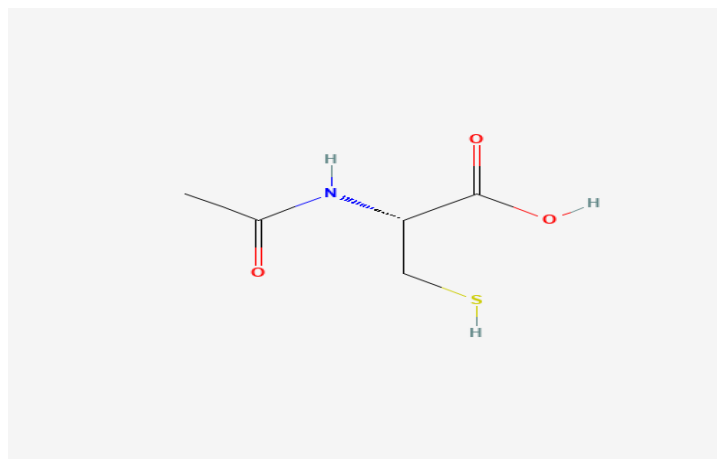


Figure 1.1: Structure of N-Acetylcysteine

Chemically, it has the formula $C_5H_9NO_3S$, with a molecular weight of $163.19 \text{ g mol}^{-1}$. Its IUPAC name is (2R)-2-acetamido-3-sulfanylpropanoic acid. The structure contains several functional groups. Especially a carboxylic acid ($-\text{COOH}$), an alcohol ($-\text{HOOCH}_3$), and a free thiol ($-\text{SH}$). With its reactivity, the thiol moiety is the principal class of nucleus responsible for free radical scavenging, reduction of disulfides, and, hopefully, recovery of endogenous antioxidant systems. The free sulfhydryl group can easily accept electrons to convert the reactive oxygen species (ROS) and reactive nitrogen species (RNS) to less reactive molecules [40–42]. Because of this, protecting cell membranes, proteins, and DNA from oxidative injury.

2.2 Pharmacology of NAC:

N-Acetyl cysteine (NAC) is synthetically derived from the natural amino acid L-cysteine. Being best known as an antioxidant, anti-inflammatory, bucolic, and cytoprotective agent, it has a range of other clinical uses. To begin with, it was merely a bucolic drug for respiratory problems [43–45]. Truth is that it is the standard antidote for acetaminophen poisoning and is just one example of its clinical uses [46, 47]. Its therapeutic effects in cardiovascular diseases, neurodegenerative disorders, metabolic diseases, cancer, and reproductive health have also been increasingly recognized lately based on several studies [27, 48].

2.2.1 Mechanism of action of NAC:

N-Acetyl cysteine (NAC) is a multifaceted antioxidant and anti-inflammatory agent that can offer substantial benefits in the treatment of diseases linked to oxidative stress and inflammation. NAC acts as a glutathione (GSH) precursor, which is the reason it helps improve the body's natural antioxidant system by increasing intracellular GSH levels and, at the same time, working directly against reactive oxygen species (ROS) [17, 37]. Also, it downplays inflammation by preventing redox-sensitive signaling pathways, particularly nuclear factor-kappa B (NF- κ B), which leads to a decrease in the release of pro-inflammatory cytokines and, at the same time, stimulates the production of antioxidant enzymes through the activation of the Nrf2 pathway [18, 36]. The sum of these effects results in safeguarding the cells against oxidative harm, maintaining cellular equilibrium, and enhancing reproductive performance in males and females.

1. Restoring the Levels of Intracellular Glutathione (GSH):

One of the main acts as an antioxidant of NAC is to support the regeneration of intracellular glutathione (GSH), which is the largest antioxidant that is naturally present in the body. Once administered, NAC is converted to L-cysteine, which is the precursor for GSH synthesis that limits the rate of production [30, 37]. NAC L-cysteine-glutamyl cysteine Glutathione (GSH) The increase of GSH leads to the scavenging

of ROS and RNS, the elimination of hydrogen peroxide and lipid peroxides via glutathione peroxidase (GPX), the replenishment of other antioxidants like vitamin C and E, and the preservation of the intracellular redox state [32, 49]. This not only counteracts oxidative damage to reproductive cells, but it also aids normal functions of ovaries and testes.

2. The Direct Scavenging of Reactive Oxygen Species:

Being equipped with a free sulfhydryl (-SH) group, NAC can directly interact with ROS and neutralize them, in particular the superoxide anions, hydroxyl radicals, hydrogen peroxide, and peroxynitrite [40–42, 50, 51]. It prevents structural changes of proteins, DNA damage, and mitochondrial dysfunction in the reproductive cells. So, the quality of the oocytes and the function of the sperm, as well as the development of the embryo, are preserved.

3. Activating the Nrf2 Antioxidant Pathways:

On top of that, NAC has been identified as a potent activator of the Nrf2 (Nuclear Factor Erythroid 2-related Factor 2) signaling pathway. It is the central antioxidant regulator in the body. Nrf2, upon activation, dissociates from its inhibitor, Keap1, in the cytoplasm and translocates into the nucleus [52]. There, it binds to the antioxidant response elements (AREs), leading to the expression of several antioxidant enzymes, including superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX), glutathione S-transferase (GST), and heme oxygenase-1 (HO-1). The existence of these enzymes collectively enhances the cellular capacity for dealing with oxidative stress and prevents reproductive tissues from long-term oxidative injury.

4. NF- κ B Suppression: NAC's major anti-inflammatory mechanism is reportedly through the downregulation of the nuclear factor-kappa B (NF- κ B) signaling pathway [18, 53]. In the presence of oxidative stress, ROS stimulates NF- κ B, which turns on the genes that encode inflammatory mediators. NAC diminishes the levels of ROS, thereby stopping the signaling and movement of NF- κ B to the nucleus. So, NAC limits the inflammatory response by lowering the levels of these mediators: Tumor necrosis factor-alpha (TNF- α) Interleukin-1 (IL-1) Interleukin-6 (IL-6) Cyclooxygenase-2 (COX-2) Inducible nitric oxide synthase (iNOS). Such a reduction in inflammation through NAC is one of the ways reproductive tissues are defended against chronic inflammatory harm.

4 Preservation of Mitochondrial Function:

Mitochondria provide ATP that is necessary for the process of oocyte maturation, sperm motility, fertilization, and embryo development [54, 55]. Mitochondrial DNA damage drops ATP output. Through this means, NAC causes mitochondria to remain in good shape: Lessen mitochondrial ROS production. Keep mitochondrial membrane potential intact. Help with ATP synthesis. Stop mitochondrial DNA damage. Better mitochondrial function is directly linked not only to the survival of reproductive cells but also to their functional capacity.

5. Prevention of Lipid Peroxidation and DNA Damage:

Gametes are highly vulnerable to oxidative damage since the sperm's membrane is packed with a lot of polyunsaturated fatty acids, while the fertilization efficacy of the oocyte is not only dependent on the surface membrane but also on the internal membranous system [56–58]. The protective roles of NAC: It prevents the following:

- Membrane lipid breakdown. - Oxidative damage to proteins.
- Scission of DNA. - Instability of chromosomes.

The ability of NAC to counteract these harmful processes enhances the quality of gametes and the potential success of fertilization and the development of an embryo.

6. Inhibition of Oxidative Stress-Induced Apoptosis:

Besides ROS being responsible for apoptosis, apoptosis can also be induced by excessive unregulated pro-inflammatory cytokines, and one of the targets of the cytokines is an activation of the mitochondrial apoptotic process. The resveratrol-mediated anti-apoptotic responses consist of:

- Upregulating Bcl-2 expressions.
- Down-regulating Bax expression.
- Blocking the activation of caspase-9 and -3.
- Stopping the release of cytochrome c.

These processes help to protect granulosa cells, Sertoli cells, Leydig cells, germ cells, and early embryos [59, 60].

7. Changes in the Reproductive Microenvironment:

Through its antioxidant and anti-inflammatory properties, NAC A LOT improves the reproductive microenvironment in ovaries, testes, endometrium, and placenta by alleviating oxidative stress and inflammation. This way, setting the perfect stage for follicular development, spermatogenesis, fertilization, embryo implantation, and fetal growth.

8. Therapeutic Potential in Reproductive Disorders:

It is the antioxidant and anti-inflammatory effects of NAC that make the drug therapeutically significant in the treatment of reproductive disorders. Studies show that in women, NAC:

- Helps to ovulate and develop follicles in PCOS conditions [24, 61, 62]. Restores balance between oxidative stress and inflammation of endometriosis sufferers.
- Doubles endometrial receptivity and embryo implantation
- Upgrades the quality of egg cells and boosts pregnancy success rates.
- Besides, NAC in men can prevent oxidative damage in the testes, overall enhancing spermatogenesis [22, 23, 63].

3. Role of NAC in female reproductive disorders:

The therapeutic potential of N-acetyl cysteine (NAC) for female reproductive disorders of female reproduction is one of the leading causes of infertility and poor pregnancy outcomes worldwide. Multiple studies show that oxidative stress, persistent inflammation, mitochondrial damage, and hormonal changes are the key factors that contribute to the development of diseases like polycystic ovary syndrome (PCOS), endometriosis, infertility issues, and pregnancy complications [8, 10, 13]. ggs, reduce the preparedness of the uterine lining for implantation, hinder embryo implantation, and interfere with a smooth pregnancy. Due to its strong antioxidant and anti-inflammatory effects, N-acetyl cysteine (NAC) is becoming recognized as a very effective drug in the field of reproductive medicine. NAC, via increasing glutathione levels inside the Cells, neutralizing reactive oxygen species, regulating inflammatory signaling pathways, and maintaining mitochondrial functions contribute to the re-establishment of cell homeostasis and lead to better reproductive results. The next parts highlight the evidence for the efficacy of NAC in treating major female reproductive disorders and its role in fertility treatments and pregnancy complications.

3.1 PCOS:

Polycystic Ovary Syndrome (PCOS) is one of the most frequent endocrine and metabolic disorders that affect women during their reproductive years [64–66]. The main features of this syndrome are hyperandrogenism (excess androgen secretion), ovulatory dysfunction, and polycystic ovarian morphology [65, 66]. PCOS is a complex disorder with various symptoms that differ from one person to another and vary with different stages of life. Besides causing reproductive problems, PCOS is now

considered a multisystem disorder that can cause metabolic, cardiovascular, psychological, and reproductive issues [64, 67–69].

Different studies estimate that PCOS affects 20% of women at reproductive age. The percentage varies per the diagnostic criteria applied and the population sampled. It causes fertility problems as well as irregular or missing menstrual cycles; it is also connected to metabolic challenges and adversely affects one's overall quality of life, which is why it is considered a serious public health issue [70, 71].

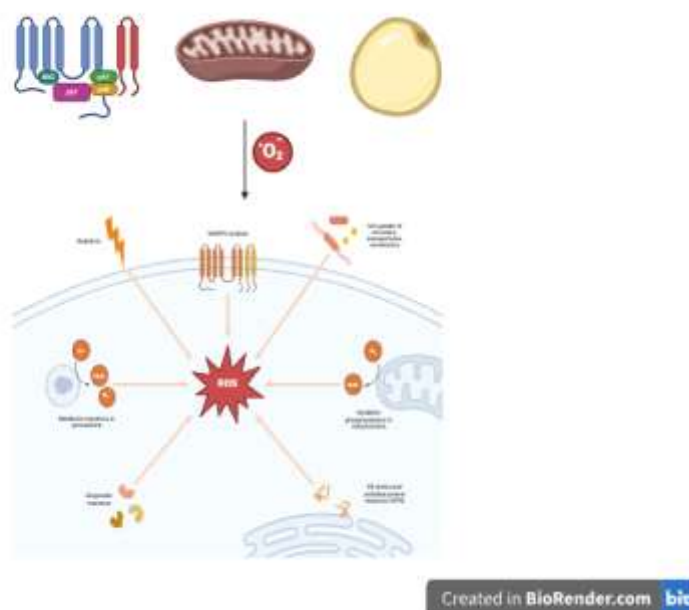


Figure 2. Mechanism of NAC in PCOS

N-acetyl cysteine (NAC), due to its antioxidant, anti-inflammatory, and insulin-sensitizing effects, has been considered an effective therapy in PCOS [20, 72, 73]. The potential role of oxidative stress in PCOS development is now more and more substantiated, and people think excess generation of free oxygen radicals for putative altered balance of reactive oxygen species (ROS) and endogenous antioxidant system might actually be responsible for some aspects of the metabolic and hormonal pathogenesis, including metabolic disturbance, ovarian steroidogenesis dysfunction, follicular development, and reproductive abnormalities [11, 52, 74]. NAC has the ability to chemically support reduced glutathione—the intracellular broad-spectrum free-oxygen-radical scavenging system. By boosting the intracellular antioxidant reserve, it may be possible to restore the redox balance in the tissues, reduce excess free oxygen radicals, and provide the tissues with protection against oxidative cell injury. Also, by lowering oxidative stress, NAC might reduce the oxidative-inflammatory synergy, which seems to underlie the persistent low-grade inflammation observed in PCOS. Enhancement of cellular redox status might also be effective on insulin response as well as on the development of the ovarian microenvironment, rather than on colliery development and ovulatory capacity. Considering then the current experience, NAC can be considered as a potential adjunctive treatment against the oxidative-inflammatory synergy that characterizes PCOS [24, 75, 76], although further evidence from large, well-designed RCTs with a long follow-up period is awaited as regards to its optimal dose and length of administration, as well as to the long-term effects on reproductive and metabolic health.

3.2 ENDOMETRIOSIS: -

Endometriosis is a chronic, estrogen-dependent inflammatory disease in which redox imbalance, immune

dysfunction, and altered cell signaling mechanisms are involved in the pathogenesis and progression of ectopic endometrial lesions [77–79]. Pro-oxidant mechanisms, including excessive generation of reactive oxygen species (ROS) and deficiency in antioxidants, can initiate and spread inflammatory signaling, cellular spread, tissue invasion, angiogenesis, and pain [12, 80–82]. N-acetyl cysteine (NAC) is a cysteine, and so reduced glutathione (GSH), a precursor, might exhibit protective effects against this definitional state through modulation of intracellular redox conditions and enhancement of the intracellular antioxidant response [83]. An elevation in intracellular GSH would positively influence the reduction in ROS, thereby limiting oxidative damage within the inflammatory milieu. Failing this, NAC has shown redox modulating and anti-inflammatory effects, some of which have been known for experimental models to involve modulation of ROS-mediated cellular spread, or TNF-, COX-2-, and matrix metalloprotease-dependent pathways [83, 84]. NAC may also have [85, 86]. or pain connected to the disease, given the involvement of oxidative stress and inflammatory mediators in peripheral and local nociceptive sensitization [85,86]. Preliminary clinical data has documented decreases in pelvic pain, dysmenorrhea, dyspareunia, analgesic intake, and endometrium size following NAC usage; still, much of this data is derived from non-randomized studies or combined antioxidant preparations [87]. And, as an antioxidant, NAC can not only improve inflammatory burden but also optimize the reproductive microenvironment, and that means improving oocyte and embryo viability and fertility potential [10, 88]. The current paucity of long-term reproductive outcome data yet precludes definitive conclusions about the effectiveness of NAC for the treatment of endometriosis and other prospective benefits.

3.3 Assisted reproductive technology (IVF/ICSI)

Assisted reproductive technologies (ART) such as IVF and ICSI are efficient methods for the treatment of infertility. Even so, oxidative stress may affect some sequential stages of the reproductive process, gamete biology, fertilization, embryo development, and implantation [7, 8, 10]. Gametes and embryos necessitate a precise redox environment in which reactive oxygen species (ROS) levels have a physiological role in cell signaling, and at the same time, ROS generation that causes oxidative damage to lipids, proteins, DNA, and mitochondria should be prevented. N-acetyl cysteine (NAC) may be important in ART because it is a cysteine precursor, which means it is a cysteine-limiting substrate used in glutathione (GSH) synthesis, one of the main cellular antioxidant molecules. GSH availability is increased, leading to an increased cellular antioxidant capacity and a redox homeostasis improvement in oocytes, spermatozoa, and developing embryos. In the female gametes, NAC administration could deficit excessive ROS production and help protect mitochondrial functions and oocyte developmental potential. In male-factor infertility, NAC may be useful to attenuate sperm membrane and DNA oxidative injury, which is relevant in ICSI given evidence that sperm DNA content may impact embryo development [57, 89, 90], y. Also, by stabilizing the redox state in the embryo culture media, NAC may hypothetically support rapid cellular growth. On endometrial effects, NAC may favorably alter the oxidative-inflammatory balance, potentially impacting the implantation process. Still, the relationship of antioxidants with ART endpoints is complex. While the currently available data does not support limited use of NAC to improve embryo quality implantation, clinical pregnancy, or live-birth rate in the general ART population, outcomes may vary per ideal patient selection and timing of administration, and responsiveness to antioxidants may be context dependent. Currently, NAC should be viewed as an intriguing redox-modulating adjunct rather than a cornerstone of ART management, with future randomized controlled trials required to evaluate optimal dose, timing, and route, at least in selected patient groups, and whether improvement in oxidative stress markers translates into improved cumulative live-birth rates.

4. Meta-analysis:

4.1 for PCOS:

N-acetyl cysteine syndrome of polycystic ovaries. One of the most studied drugs for PCOS is N-acetyl cysteine. The effects of this antioxidant have been considered both in the ovulatory and in the metabolic parameters of women with PCOS, acting as an antioxidant as it is considered a precursor in the synthesis of glutathione. The use of N-acetyl cysteine increased a lot the number of women with ovulation in comparison with placebo [24, 61, 62].

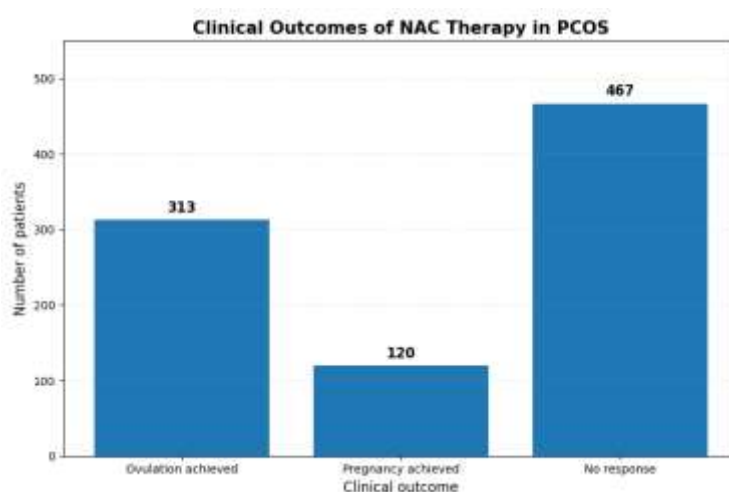


Figure 3. Clinical outcome of NAC therapy in PCOS

N-acetyl cysteine (NAC) has been studied in PCOS because of its antioxidant, glutathione-restoring, insulin-sensitizing, and anti-inflammatory properties. PCOS is related to oxidative stress and chronic low-grade inflammation, which are implicated in unusual folliculogenesis, insulin resistance, hyperandrogenic biochemistry, and ovulatory infertility. A systematic review and meta-analysis of randomized controlled trials, including 8 studies and 910 women with PCOS, compared the effects of NAC versus controls [24]. NAC improved reproductive outcomes versus placebo, mostly pregnancy and ovulation. In pooled analyzes, women receiving NAC were more likely than controls to ovulate (OR 3.13, 95% CI 1.54-6.36), with an even larger positive effect size noted among women with clomiphene-resistant PCOS (OR 8.40, 95% CI 4.50-15.67). Significant mix was evident in some analyses, particularly in women resistant to camphene. NAC had variable effects on BMI and testosterone and various measures of insulin resistance, menstrual function, hirsutism, and acne compared to placebo. In head-to-head comparisons, metformin had greater effects than NAC on reproductive and metabolic parameters [72]. Current evidence does not suggest that NAC can be regarded as a definitive treatment. Yet NAC can be an adjuvant antioxidant therapy in the management of PCOS.

4.2 For Endometriosis:

N-acetyl cysteine (NAC) is emerging as a non-hormonal adjunctive modality in the treatment of endometriosis because of its glutathione-replenishing, antioxidant, redox-modulating, and anti-inflammatory effects [83, 87]. A systematic review published in 2026 identified 22 studies examining NAC in endometriosis, of which six were clinical studies; other references were experimental and translational studies. The clinical evidence supports a role for NAC to reduce pain, reduce analgesic

requirements, and induce or maintain the reduction of ovarian endometriosis in some selected non-postoperative endometriosis patients.

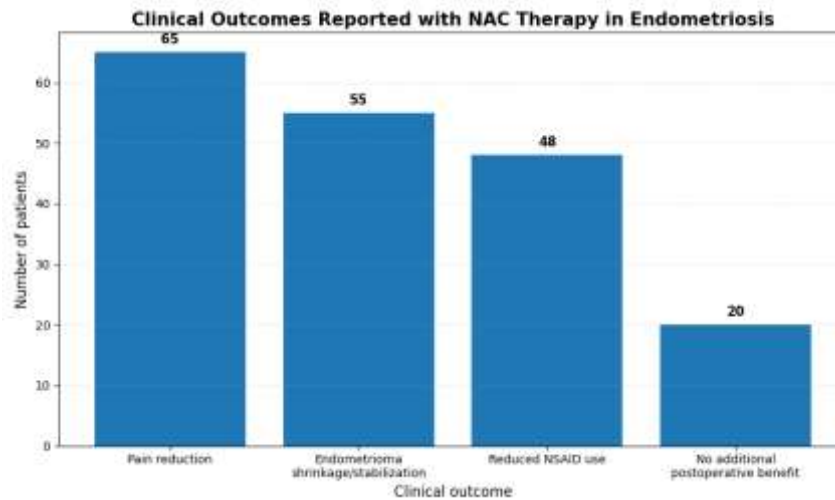


Figure 4. Clinical outcome in endometriosis

In a prospective single-cohort study of 120 women, 600 mg three times daily of NAC over three consecutive days per week for three months provided significant reductions in dysmenorrhea, dyspareunia, chronic pelvic pain, NSAID use, endometrium size, and serum CA-125 [87]. Of 52 women desiring pregnancy, 39 conceived after six months, although as the study did not include a control group, causality cannot be attributed to NAC. Conversely, a randomized postoperative investigation of women following conservative laparoscopic treatment found no significant additional benefit of adding NAC on endometrium recurrence or pelvic pain reductions beyond oral contraceptive therapy (OC) alone. Investigations of combination antioxidant formulations that include NAC have shown significant pain reductions, but these cannot be definitively ascribed to the impact of NAC independent of other intervening antioxidants. Preclinical data shows available robotic evidence with potential reductions in reactive oxygen species and inflammatory mediators, cellular rapid growth, lesion burden, and migration factors and argues for the role of TNF-, COX-2, MMP-2/MMP-9, and redox-sensitive pathways [83, 84]. Though, due to the large variety in study methods, NAC regimens, patient cohorts, comparators, and tested outcomes, the evidence base cannot currently be pooled quantitatively.

4.3 for Assisted Reproductive Technology (IVF/ICSI):

Assisted reproductive technology (ART) has a number of stages that are affected by oxidative stress, namely follicular development, oocyte maturation, fertilization, and embryo development [7, 8, 10]. There are physiological effects of reactive oxygen species in fertility, but overproduction could bring lipid peroxidation, mitochondrial damage, DNA abnormality, and reduced gamete and embryo quality. N-acetyl cysteine (NAC) is a precursor of the sulfur-containing amino acid glutathione, which has been studied as an adjunct to ART. NAC would increase cysteine levels and promote the production of glutathione, improving endogenous antioxidant systems.

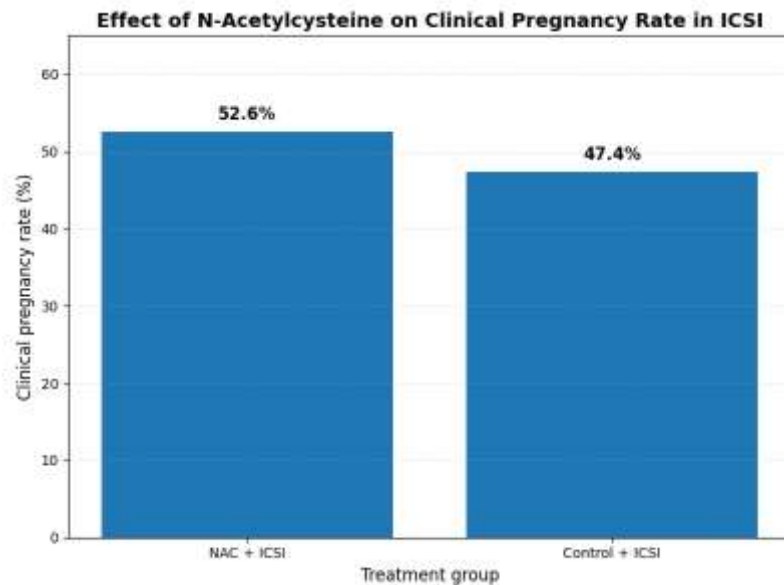


Figure 5. Effects of NAC on clinical pregnancy rate in ICSI

Preliminary clinical data offer evidence for effects on selected laboratory ART endpoints. In a randomized placebo-controlled pilot trial of 60 women with polycystic ovarian syndrome undergoing ICSI, those treated with 1,800 mg/d NAC for an average of six weeks had fewer juvenile and unusual oocytes, a larger number of good-quality embryos, and lower concentrations of malondialdehyde in the culture medium than those receiving placebo [21]. While promising, this study was small and performed in a specific patient population; further trials are needed to evaluate the potential utility of NAC in the general ART patient population. In a separate randomized controlled trial of 76 women with ICSI for male factor infertility, clinical pregnancy was achieved in 52.6% of those receiving NAC compared to 47.4% in the control group ($P=0.557$); no statistical difference in blastocyst formation following treatment with NAC in women of advanced reproductive age, the number of high-quality blastocysts was increased in the NAC group, but clinical pregnancy rates did not achieve significance.

Further studies have also looked at combinations of antioxidants containing NAC but not NAC alone. The effects have been reported on embryo development, but it is unclear what NAC's effects are when it has been tested in combination with compounds like acetyl-L-carnitine or -biopic acid. A recent large, randomized trial of an antioxidant mixture including N-acetyl-L-cysteine in embryo culture media failed to show an effect on clinical pregnancy, highlighting the importance of separating the effects of NAC alone from combined antioxidant studies. For this reason, evidence from mixed antioxidant mixtures should not be extrapolated to evidence for NAC alone.

The possible benefit of NAC treatment for male-factor infertility is also pertinent to ICSI, as excessive sperm oxidative stress can compromise membrane integrity, mitochondrial function, motility, and DNA integrity [57, 58, 91]. Meta-analyses of NAC treatment of idiopathic male infertility have shown improvements in sperm concentration, motility, morphology, and embryonic volume [22, 23, 63, 92], SI live-birth rates. So, the male reproductive literature can be used to support NAC treatment in ART but should not be considered as a direct comparison. All in all, there is a biologically plausible role for NAC in ART by antioxidative glutathione-dependent effects and the attenuation of excess ROS. Clinical data show some evidence of potential efficacy on oocyte and embryo quality in some specific subgroups, whereas information on clinical pregnancy and live birth is mixed. The meta-analysis of oral antioxidants in IVF/ICSI embryo transfer (ET) showed higher clinical pregnancy, mature oocyte numbers, high-quality

embryos, and live birth; yet the data was combined with multiple antioxidant agents and so cannot be applied directly to NAC. Larger randomized controlled trial data with clearly described doses and durations of treatment with clinically meaningful endpoints (live birth) is because of this; it should be combined with oxidative-stress biomarkers such as malondialdehyde and glutathione with reproductive outcomes.

5. Conclusion:

N-acetyl cysteine is a potential novel adjunct in female reproductive therapeutics given its antioxidant, glutathione-recovering, and anti-inflammatory capacities. Through reducing an oversupply of reactive oxygen species and inhibiting redox-sensitive inflammatory signaling, NAC can impact many aspects of reproductive pathology, including oxidative stress, insulin resistance, unusual folliculogenesis, endometrial receptivity, and tissue remodeling.

The current body of evidence appears to be most supportive of a potential role for NAC in the setting of polycystic ovary syndrome, with recent meta-analytical evidence supporting improvements in certain reproductive parameters, including progesterone and endometrial thickness. Still significant variety between studies and divergent findings across various hormonal and metabolic endpoints should lead to the conclusion that NACS should be (now) regarded as an adjunct to, and not as an alternative to, established therapies for PCOS. In the setting of endometriosis, the body of evidence (despite significant mix) from studies of rigid, preclinical, and emerging clinical evidence would also support a potential role for NAC to improve pain and endometrium-related outcomes, and although the evidence from clinical studies is promising, it remains limited. When considering the current evidence related to fertility (including the use of IVF/ICSI treatment), the evidence in support of improved outcomes is again promising but limited.

Comparative Clinical Outcomes of NAC Therapy

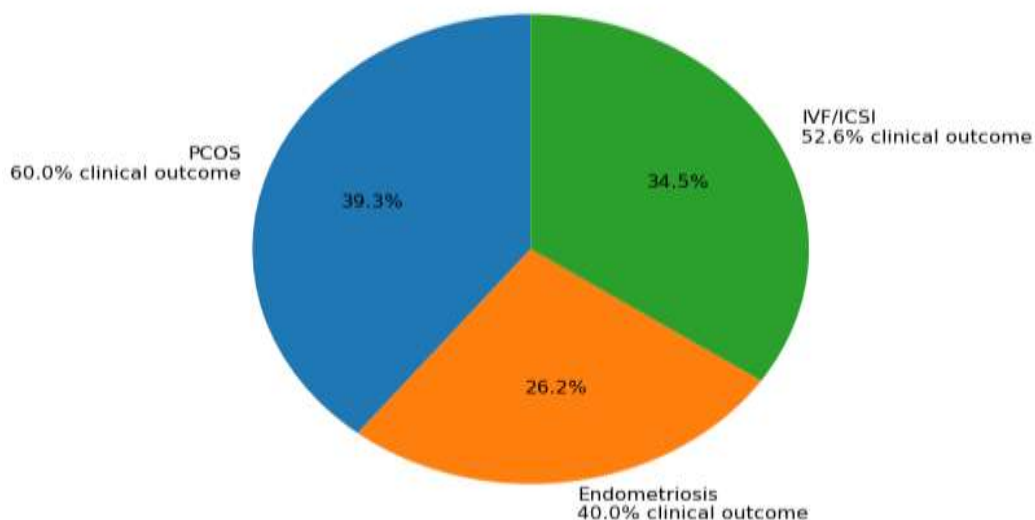


Figure 6. Comparison of clinical outcomes of NAC therapy

NAC should not be viewed as a treatment for PCOS, endometriosis, or infertility but is more likely to have an adjunctive role for the treatment of inflammation and oxidative stress that are prevalent with these conditions. Adequately powered multicenter RCTs of different doses and durations of NAC and uniform criteria of patient selection are needed. Future research should also extend to clinically relevant outcomes

that matter to patients, including ovulation, clinical pregnancy implantation, ongoing pregnancy, live birth, endometriosis pain, recurrence, and adverse events, with appropriate long-term follow-up. With the standardization of endpoints in various patient groups, it remains to be determined which conditions and subgroups benefit most from NAC treatment.

On balance, the existing evidence this way far suggests NAC as a biologically plausible and potentially useful* adjunctive antioxidant and anti-inflammatory approach in female reproductive health. But further, robust clinical evidence is required to define its standard therapeutic role.

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