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Oxidative Stress Factors is Effective on Reproductive Functions: A Review

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ABSTRACT

Oxidative stress (OS) results from an imbalance in the production of reactive oxygen species (ROS) and antioxidant defenses, leading to cellular damage, caused by excess ROS. OS is mediated by free radicals, such as ROS or reactive nitrogen species produced during physiological aerobic metabolism and pathological inflammatory processes. OS causes damage to cellular components, inactivation of essential metabolic enzymes and disruption of signal transduction pathways.

OS has been shown to play an important role in the pathogenesis of subfertility in both men and women. OS has been associated with a number of reproductive diseases such as endometriosis, polycystic ovary syndrome and unexplained infertility. Pregnancy complications, such as spontaneous abortion, recurrent pregnancy loss and pre-eclampsia may also develop in response to OS. Antioxidant supplementation may be effective in controlling ROS production and continues to be explored as an option to overcome reproductive disorders associated with infertility.

Keywords: Antioxidants, female infertility, oxidative stress, reactive oxygen species

INTRODUCTION

Oxygen (O_2) is essential for aerobic life and oxidative metabolism is the main source of energy. Cells have a defense system against reactive oxygen species (ROS) under aerobic conditions and there is a homeostasis between pro-oxidants and antioxidants for healthy biology. Oxidative stress (OS) occurs with excessive ROS production or when the anti-oxidant defense mechanisms are weakened.[1,2] The most biologically important ROS are superoxide anion (O_2--), hydroxyl radical (-OH), peroxyl, alkoxyl and hydroperoxyl. Free radical species are unstable and highly reactive, but can become stable by taking electrons from lipids, nucleic acids, proteins, carbohydrates or other nearby molecules, causing chain reactions and leading to cellular damage and disease.[3] Therefore, OS can cause DNA damage, lipid peroxidation and also protein damage. Under normal conditions, there are two types of antioxidants in the body; non-enzymatic antioxidants and enzymatic antioxidants. Enzymatic antioxidants include superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase (CAT) and glutathione reductase (GSR), which can cause the reduction of hydrogen peroxide (H_2O_2) to water and alcohol. Non-enzymatic antioxidants are synthetic antioxidants or dietary supplements containing vitamin C, vitamin E, β-carotene, selenium, Zn, taurine, glutathione (GSH) and the like.[4]

OS is thought to be responsible for the initiation or development of pathological processes[5] affecting female reproduction, such as embryonic resorption, recurrent pregnancy loss, preeclampsia, intrauterine growth restriction and fetal death.[6] A non-pathological level of ROS is an important regulator of folliculogenesis, corpus luteum oocyte maturation and feto-placental development through various signaling pathways.[7] However, ROS can sometimes exert deleterious effects when present in excessive amounts. Thus, ROS have a close relationship with reproductive events. Excessive ROS may lead to multiple reproductive problems, including endometriosis, polycystic ovary syndrome (PCOS) and unexplained infertility.[8] Is also a central element of cell signaling, gene expression and signal transduction pathways involved in cell function, growth, differentiation and death.[9] Therefore, tightly controlled ROS

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production is important for normal function and good health.

Reactive Oxygen Species and Their Physiological Actions

ROS are produced during O_2 consumption.[10] ROS are composed of free and/or non-free radical intermediates, with free radicals being the most reactive. This reactivity is due to one or more unpaired electrons in the outer shell of the atom. In addition, O_2- and nitrogen-dependent biological processes are of greater importance because their end products are often found in pathological processes or in situations of high metabolic demand in external environmental interactions.[1]

Biological systems contain large amounts of O_2. As a radical, O_2 reacts rapidly with other radicals. Free radicals are usually produced from O_2 itself and partially reduced species originate from normal metabolic processes in the body. ROS are prominent and potentially toxic intermediates commonly found in OS.[11]

The Haber-Weiss reaction, given below, is the main mechanism by which the highly reactive hydroxyl radical (OH*) is produced. This reaction can generate more toxic radicals through interactions between the superoxide (SO) anion and H_2O_2. There are three main types of ROS: superoxide anion (O_2--),H_2O_2 and hydroxyl (-OH).[11,12]

$O+-2+H_2O_2>O_2+OH-+OH^*$

However, this reaction has been found to be thermodynamically inefficient in biological systems.

The Fenton reaction, which consists of two reactions, demonstrates the use of a metal ion catalyst to produce OH* as shown below.[11]

$Fe_3++O.-2>Fe_2++O_2$

$Fe_2++H_2O_2>Fe_3++OH-+OH^*$

Most ROS are produced when electrons leak from the mitochondrial respiratory chain, also called the electron transport chain (ETC).[10] According to one study, up to 2% of the O_2 consumed by mitochondria can be diverted to ROS formation, especially in complexes I and III.[13] The free radical superoxide anion (O_2--) is formed when an electron is added to ground state dioxygen, but is unstable in aqueous solutions because it can react spontaneously to produce H_2O_2 and molecular O_2. It can reduce Fe_3+ to Fe_2+ and convert to O_2. H_2O_2 is not a free radical, but it is highly damaging to cells as it can cross biological membranes and convert to the highly reactive -OH.[14]

Physiological processes that utilize O_2 as a substrate, such as oxygenase reactions and electron transfer reactions, produce large amounts of ROS, the most common of which is the SO anion.[15]

Other sources of SO anion include the short electron chain in the endoplasmic reticulum, cytochrome P450 and the enzyme nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, and other oxido-reductases that are produced in excess, especially in early pregnancy.[1,10]

Mitochondria are of central importance for metabolic activities in cells, so a disruption in their function can cause significant alteration in adenine triphosphate (ATP) production. The energy derived from ATP is essential for gamete function. Although mitochondria are the main sites of ROS production, excess ROS can alter the function of mitochondria in oocytes and embryos. This mitochondrial dysfunction can cause cell division arrest triggered by OS.[16] A slight increase in ROS levels stimulates cell growth and proliferation and allows normal physiological processes. Conversely, excess ROS causes cellular damage (e.g., damage to DNA, lipid membranes and proteins).

Reactive Nitrogen Species

Reactive nitrogen species (RNS) include nitric oxide (NO) and nitrogen dioxide in addition to non-reactive species, such as peroxynitrite (ONOO-) and nitrosamines. Peroxynitrite may induce lipid peroxidation and nitrozation of many tyrosine molecules that normally act as mediators of enzyme function and signal transduction.[17]

NO is a free radical with vasodilatory properties. Although the vasodilatory effects of NO can be therapeutic, excessive RNS production can affect protein structure and function. NO-related effects have also been suggested to occur through ROS production through the interaction between NO and the SO anion. In the absence of L-arginine[17] and in sustained low antioxidant states, intracellular production of SO is increased. Elevated SO anion levels promote reactions between peroxynitrite formation and NO, which exacerbates cytotoxicity.[18]

The enzyme nitric oxide synthase (NOS) uses NADPH as an electron donor, catalyzes NO formation from O_2 and L-arginine[19] and is composed of the following isoforms: neuronal NOS (nNOS or NOS I), inducible NOS (iNOS or NOS II) and endothelial NOS (eNOS or NOS III). The nNOS isoform is a neurotransmitter and iNOS is expressed primarily in macrophages following induction by cytokines. eNOS activity increases in response to luteinizing hormone (LH) surge and human chorionic gonadotropin.[10] In general, NO produced by eNOS and nNOS regulate physiological functions, whereas NO production by iNOS appears to be more active in pathophysiological conditions.

Antioxidant Defense Mechanisms

The enzymatic antioxidants SOD, GPx, CAT and GSR all function as endogenous elements of the primary antioxidant defense mechanism. SOD catalyzes O_2-- dismutation to produce H_2O_2 and O_2 at a rate 104-fold higher than normal dismutation at physiological pH.[20] CAT serves to remove H_2O_2 from the cell when H_2O_2 is in high concentrations. GPx catalyzes the reduction of H_2O_2 and organic free hydroperoxides but requires GSH as a co-substrate. GSR is a cytosolic protein with a tissue distribution similar to that of GPx. GSR also reduces oxidized GSH using NADPH produced by various systems.[7,21]

Non-Enzymatic Antioxidants

Non-enzymatic antioxidants consist of metabolites absorbed from the diet or synthetic antioxidant compounds, including vitamin C, GSH, taurine, hypotaurine, vitamin E, zinc (Zn), selenium, beta-carotene and carotene.[22]

Vitamin C (ascorbic acid) is a redox catalyst that is involved in the neutralization of ROS by reduction. Its reduced form is protected by reactions with GSH and can also be catalyzed by the enzyme disulfide isomerase and glutaredoxins.

GSH is a peptide made in the cytosol from cysteine, glutamate and glycine and is present in most forms of aerobic life.[23] Of note, it is also the main non-enzymatic antioxidant found in oocytes and embryos. The source of its antioxidant property is the thiol group of its cysteine component, which is a reducing agent that allows it to be reversibly oxidized and reduced to its stable form.[24] GSH levels are regulated by *de novo* formation catalyzed by the enzymes gamma-GCS and GSH synthetase.[2] GSH participates in multiple reactions, including the formation of GSH disulfide, which is converted back to GSH by GSR at the expense of NADPH.[21]

Cysteine and cysteamine (CSH) increase the GSH content of the oocyte. CSH also acts as a scavenger and is necessary to maintain high GSH levels. CSH can also be converted to hypotaurine, another antioxidant. The concentrations of many amino acids, including taurine, vary significantly during folliculogenesis. Taurine and hypotaurine are scavengers that help maintain redox homeostasis in the gametes.[24]

Vitamin E, the major lipid-soluble vitamin found in all cell membranes, provides effective protection against lipid peroxidation. The tocopheryl radical can be directly reduced by a ascorbic acid-GSH redox couple. β-carotene shows the most effective scavenging effect, together with vitamin E, but β-carotene is more effective at low O_2 pressures. However, vitamin E prevents oxidation of the conjugated double bonds of β-carotene.[14]

Unlike vitamins C and E and GSH, the hormone melatonin is an antioxidant that can be produced by the human body. However, it cannot enter the redox cycle like other antioxidants; once oxidized, melatonin cannot return to its reduced state. It forms stable end products after the reaction. The iron-binding proteins transferrin and ferritin prevent the catalysis of free radicals through chelation and play an important role in antioxidant defense.[25] Although nutrients such as Se, copper (Cu) and Zn do not have antioxidant effects, they are necessary for the activity of some antioxidant enzymes.

Oxidative Stress and Antioxidant Capacity in the Male Reproductive System

Almost half of infertility cases may be due to male reproductive pathologies, which can be congenital or acquired.[26] In men, the role of OS has long been recognized as a major contributing factor to infertility. Men with high OS levels or DNA-damaged sperm are more likely to experience infertility. The key determinants of fertilization capacity are sperm count and motility. These key factors can both be impaired by ROS.[27]

There is much evidence to support the role of ROS in male infertility.[28,29] Spermatozoa have a unique plasma membrane structure that contains significant levels of polyunsaturated fatty acids that also increase membrane flexibility, which is essential for oocyte penetration. Unfortunately, this membrane is highly vulnerable to ROS attack.[29,30] The precise reaction appears to be a cascade of lipid peroxidation that compromises membrane cell integrity, causing a decrease in sperm motility and subsequent reduced fertility. In addition, ROS also lead to significant DNA damage.[31]

Natural antioxidants in the human body include vitamins C and E, SOD, thioredoxin and GSH. These antioxidants can neutralize free radical activity and protect spermatozoa from ROS.[32] There may be lower concentrations of antioxidants in the semen of infertile men. This may explain the high levels of ROS in the semen of infertile men compared to fertile men. Sperm function tests such as sperm DNA fragmentation and OS measurements are widely used to provide a better understanding of true male fertility potential.[33]

Semen analysis may show the following pathologies: asthenospermia (reduced motility), oligozoospermia (low sperm count) and teratozoospermia (abnormal morphology) or a combination of all of these (WHO 2021 classification). The WHO 2021 guidelines recommend the standard values of sperm parameters are: total sperm count 39 million or more per ejaculate; sperm concentration ≥16 million/mL; sperm volume 1.4 mL or more; progressive sperm motility 30% or more; and normal morphology 4% or more.[34]

DISCUSSION

Vitamin C acts as an important co-factor in hydroxylation and amidation reactions and is a water-soluble antioxidant.[35] Together with vitamin E, it plays an important role in collagen synthesis, proteoglycans and intercellular matrix.[36] Vitamin C is found in high concentrations in seminal fluid.[37]

Greco et al.[38] reported an intervention study with men suffering from infertility. In this study, the intervention group received one gram of vitamin E and one gram of vitamin C. After two months, there was a significant reduction in the degree of DNA damage in the intervention group ($p<0.001$). However, no positive correlation was found between vitamin E and C treatment and the key semen parameters, motility and concentration. In a second study by these authors, intracytoplasmic sperm injection and in vitro fertilization show that a significant proportion of sperm DNA damage leads to lower infertility rates using the same antioxidant supplementation as in the earlier study (vitamin E 1 g and vitamin C 1 g).[38] Moslemi and Tavanbakhsh[39] performed a study with 690 infertile men with idiopathic Oligoasthenoteratozoospermi (OAT) receiving daily antioxidant supplementation with selenium (200 μg) in addition to vitamin E (400 IU). Supplements were given for at least 100 days. The authors reported an overall improvement in sperm motility, morphology, or both in 52.6% (362 cases) and a spontaneous pregnancy rate of 10.8% (75 cases) compared to men receiving no treatment.

L-carnitine (LC) (3-aminobutyric acid) is present in the human body and is also a metabolized vitamin. The participation of LC in intermediary metabolism is essential and plays an important role in the formation of acyl carnitine esters.[40] High concentrations of LC in the human body are 2000 times higher in the epididymis than in serum.[41]

To date, few studies have investigated the effect of LC supplementation. Lenzi et al.[42] reported a double-blind controlled clinical trial on the effect of LC on male infertility. In

this study, 60 infertile men with OAT were treated, divided into intervention and control groups. Patients in the intervention group received 2 g/day LC and 1 g/day L-acetyl carnitine (LAC) for six months. A positive association between LC and LAC supplementation and sperm motility was observed in the study population. Interestingly, this association was more significant with lower sperm motility at baseline sperm quality assessment. Garolla et al.[43] reported the effect of LC treatment and phospholipid hydroperoxide glutathione peroxidase (PHGPX) treatment in men with OAT. In this study, 30 men with idiopathic OAT were treated in a double-blind study. They formed two patient groups. One group of patients was treated with placebo for three months followed by 2 g LC daily for another three months. Those receiving LC treatment showed improvement in sperm motility when there was normal PHGPX levels.

Co-enzyme Q10 (CoQ10, also known as ubiquinone) is another antioxidant supplement. As an ETC component, it is involved in aerobic cellular respiration producing cellular energy compounds such as ATP. Balercia et al.[44] reported the effect of CoQ10 on sperm motility in infertile men. In their study, 60 men with idiopathic OAT received CoQ10 treatment in a double-blind controlled trial. After six months of treatment, the CoQ10 content in the ejaculate of patients receiving CoQ10 increased and sperm motility also improved. Six spontaneous pregnancies occurred in the CoQ10-treated patient group, while three spontaneous pregnancies occurred in the placebo group. Thakur et al.[45] reported that 150 mg CoQ10 daily administration improved semen parameters in oligospermic men.

Zn is the most abundant metal in the body after iron. Zn is known as a metal that plays an important role in testicular development and sperm maturation. Studies have shown that Zn supplementation has a protective effect on spermatozoa against oxidized thiol levels and therefore may improve impaired semen function. Alsalman et al.[46] reported that oxidized thiol levels and semen returned to normal in a study of 60 infertile men receiving 220 mg Zn sulfate daily for three months.

Low sperm Zn concentrations are associated with low sperm fertilization capacity. Ebisch et al.[47] reported on men taking 26 mg Zn and 66 mg folic acid for five weeks. These authors reported an improvement in sperm concentration. However, they did not observe any improvement in other sperm parameters. In contrast to baseline, a positive correlation was found between motility, serum sperm concentration, inhibin B levels and Zn.

Selenium has been shown to be an essential trace element for testosterone biosynthesis and sperm formation.[48]

N-acetylcysteine (NAC) is a naturally occurring compound. It is a reaction product of the amino acid L-cysteine and functions as a precursor of GPx. Randomized clinical trials have reported that selenium supplementation, alone or in combination, improved sperm count, motility and morphology, and sperm concentration in men suffering from infertility.[49,50] Safarinejad and Safarinejad.[49] studied the effect of selenium and NAC in 468 infertile men with idiopathic OAT. The patients were followed for a period of 30 weeks. Serum follicle stimulating hormone (FSH) decreased, while serum testosterone and inhibin B levels increased. As a result, all semen parameters improved in the treated population. In addition, selenium plus NAC administration significantly improved semen parameters.

Paradiso Galatioto et al.[51] reported a study to determine the effectiveness of antioxidant supplementation on semen parameter quality and natural pregnancies in men with infertility, six months after retrograde varicocele treatment. Twenty men with varicocele received antioxidant supplementation treatment: NAC and a cocktail of vitamins and minerals (vitamin E, vitamin C, vitamin A, thiamine, biotin, B12, riboflavin, magnesium, Fe, Cu, manganese, Zn). A significant increase in sperm count was reported in the treated population. However, no significant association was found between multiple supplement treatment and other sperm parameters, including morphology and motility.

Tremellen et al.[52] reported a prospective, double-blind, randomized, placebo-controlled study involving 60 couples with infertility. Patients were randomly assigned to a treatment group receiving a capsule containing 6 mg Lycopene, 500 mg vitamin C, 400 IU vitamin E, 26 micrograms Se, 25 mg Zn, 5 mg folate and 1000 mg garlic or placebo daily for three months. The antioxidant group showed a significant improvement in successful pregnancy rate (38.5%) compared to the control group (16%). There was no significant difference in oocyte fertilization rate and embryo quality between the two groups.

Sengupta et al.[53] 2022 reported that intense antioxidant supplementation may lead to excessive reducing substances and negatively affect fertility by disrupting key oxidation mechanisms in homeostasis.

Sadeghi et al.[54] 2022 also focused on the balance between oxidative and reductive stress in terms of sperm integrity. According to their research, intense supplementation may increase reductive stress, which leads to impaired sperm function and therefore may be counterproductive.

Oxidative Stress and Antioxidant Capacity in the Female Reproductive System

Each month, a group of oocytes begins to grow and develop in the ovary, but in only one, the dominant oocyte, meiosis I continues. This process is determined by an increase in ROS and is inhibited by antioxidants. In contrast, the progression of meiosis II is enhanced by antioxidants[23], suggesting a complex relationship between ROS and antioxidant homeostasis in the ovary. The increase in steroid production in the growing follicle causes an increase in cytochrome P450, leading to ROS production. ROS produced by the oocyte before ovulation are suggested to be important inducers of ovulation.[2] O_2 deficiency stimulates follicular angiogenesis, which is important for adequate growth and development of the ovarian follicle. Follicular ROS promote apoptosis, whereas GSH and follicular FSH balance this effect in the growing follicle. Estrogen increases in response to FSH, triggering CAT formation in the dominant follicle and thus preventing apoptosis.[23]

ROS have both negative and positive effects on mammalian ovaries.[27] ROS cause many different physiological and

pathological activities in the ovaries from oocyte maturation to fertilization. In cyclic oocytes, different markers of OS are negatively affected.[55] ROS concentrations may also play an important role in implantation and fertilization of oocytes, and a related study described the localization of SOD in the ovary and reported that Cu-Zn SOD was localized in the granulosa cell of growing follicles and mature Graafian follicles, while manganese SOD (MnSOD) was localized in the luteal cells of the corpus luteum in rats.[23]

A rapid decrease in progesterone is required for adequate follicle development in the next cycle. Cu-Zn SOD increases in the corpus luteum during the early and mid-luteal phase and decreases during the regression phase. This activity parallels the change in progesterone concentration, in contrast to the increased lipid peroxide levels during the regression phase.

Other possible explanations for the decrease in Cu-Zn SOD are increased prostaglandin (PG) F2-alpha or macrophage activity or decreased blood flow in the ovary.[23] PG F2-alpha induces SO anion production by luteal cells and phagocytic leukocytes in the corpus luteum. Reduced blood flow in the ovary causes tissue damage through ROS production. During regression, Mn SOD concentrations in the corpus luteum increase to scavenge ROS produced in the mitochondria by inflammatory reactions and cytokines. Complete breakdown of the corpus luteum causes a significant decrease in Mn SOD in the regressing cell. At this point, cell death is inevitable.[25] Cu-Zn SOD is closely associated with progesterone production, while Mn SOD protects luteal cells from OS-induced inflammation.[23]

OS affects the entire reproductive process throughout a woman's life. ROS attack the eighth carbon atom of guanine in DNA, producing 8-hydroxy-deoxyguanosine (8-OHDG), an oxidized deoxyguanosine which is present in higher concentrations in aging oocytes.[56] 8-OHDG is the best known base modification in mutagenic damage. 8-OHDG causes base mutation and mismatches in DNA replication and leads to the conversion of G mutations to T and G:C to T:A. Therefore, 8-OHDG has become a biomarker for OS.

OS is implicated in many female diseases, including PCOS, the most common endocrine abnormality in women of reproductive age, with a prevalence of approximately 18%. PCOS is characterized by hyperandrogenism, ovulatory dysfunction and polycystic ovaries.[57] Several studies have shown the presence of OS in PCOS patients. In a study by Costello et al.[58] increased serum prolidase activity, as well as higher total oxidant status and OS indices, the ratio of oxidants to total antioxidant status (TAS), were found in PCOS patients. Decreased mitochondrial O_2 consumption and GSH levels, together with increased ROS production, may explain mitochondrial dysfunction in PCOS patients. Physiological hyperglycemia produces increased levels of ROS from mononuclear cells, which activates the release of the cytokine tumor necrosis factor-α (TNF-α) and increases the inflammatory transcription factor nuclear factor-kappa B (NF-κB). As a result, TNF-α concentrations, a known mediator of insulin resistance, are further increased. The resulting OS creates an inflammatory environment that further promotes insulin resistance.[58]

Bremer and Miller.[59] reported that disruption of the delicate balance between intra- and extra-ovarian factors interferes with mature oocyte formation and leads to infertility. Furthermore, insulin plays a special role in PCOS and *in vitro* studies have reported that insulin stimulates proliferation of protozoa, increases secretion of androgens mediated by LH and increases cytochrome P450 expression of the LH and IGF-1 receptor.[59] Cytochrome P450 is weel known to be able to increase ROS concentrations. This evidence suggests that ROS participate in the pathological process of PCOS.

Endometriosis is a benign, estrogen-dependent, chronic gynecological disease characterized by the presence of endometrial tissue outside the uterus. Lesions are usually found on dependent surfaces in the pelvis. They can also be found in other sites, such as the intra-abdominal organs, lungs and urinary tract. Endometriosis affects 6% to 10% of women of reproductive age and is also known to be associated with pelvic pain and infertility[60], but it is a complex and multicomponent disease that cannot be explained by a factor but is the result of a multifactorial pathogenetic mechanisms. These include retrograde menstruation, impaired immunologic response, genetic predisposition and inflammatory components.[61] The most likely mechanism explaining pelvic endometriosis is the retrograde menstruation and implantation theory. This theory suggests that the reflux of endometrial tissue from the fallopian tubes during menstruation explains its extra-tubal localization and adhesion to the pelvic viscera.[62]

Studies have reported mixed results regarding the detection of OS markers in patients with endometriosis. Some studies have not reported increased OS in the peritoneal fluid or circulation of patients with endometriosis[63], while others have reported increased levels of OS markers in those with the disease. Proinflammatory and chemotactic cytokines play a central role in the recruitment and activation of phagocytic cells, which are a major source of both ROS and RN.[64]

2010 measured *in vivo* peritoneal fluid and plasma 8-iso-PGF2-alpha levels in patients with endometriosis. They found that 8-iso-PGF2-alpha levels in both urine and peritoneal fluid of patients with endometriosis were significantly higher compared to control measurements.[65] 8-iso-PGF2-alpha levels are likely to be useful in predicting oxidative status in diseases, such as endometriosis, and may also be helpful in determining the cause of concurrent infertility.

Patients with endometriosis are more likely to have lower pregnancy rates compared to those without endometrosis. In addition to spermatotoxic peritoneal fluid, ROS may mediate poor oocyte and embryo quality and may also contribute to the subfertility experienced by patients with endometriosis.[66] The peritoneal fluid of women with endometriosis contains low concentrations of the antioxidants vitamin C[64] and GPx.[67] The decrease in GPx levels is thought to be due to a reduced response of endometrial cells to progesterone.[68]

Unexplained infertility is defined as the inability to conceive after 12 months of unprotected intercourse in couples where known causes of infertility have been assessed and no impairments have been identified. It is therefore considered a diagnosis of exclusion. Its pathophysiology remains

unclear, but the literature suggests a possible contribution of increased levels of ROS, indicated by increased levels of the lipid peroxidation marker malondialdehyde (MDA), especially compared to the concentration of antioxidants in the peritoneal cavity.[69] Increased amounts of ROS in these patients suggest a decrease in antioxidant defenses, including GSH and vitamin E. The low antioxidant status of peritoneal fluid may be a determining factor in the pathogenesis of idiopathic infertility.

Folate (vitamin B9) is considered indispensable for reproduction. It is involved in amino acid metabolism and methylation of proteins, lipids and nucleic acids. Acquired or inherited folate deficiency contributes to homocysteine accumulation. Recently, Altmäe et al.[70] reported that the most important variation in terms of effect on folate metabolism is the *methyl-tetra-hydrofolate reductase (MTHFR)* gene polymorphism 677C/T.

Pregnancy is a state of OS caused by increased metabolic activity in placental mitochondria and increased ROS production due to the higher metabolic demands of the growing fetus.[71] SO anions produced by placental mitochondria are thought to be the main source of ROS and lipid peroxidation contributing to OS in the placenta and are supported by mitochondrial production of lipid peroxides, free radicals and vitamin E in the placenta, which increases as the pregnancy progresses.[72] In the second trimester, the placenta gradually matures and increases in size with less hair and larger blood vessels. The cytotrophoblast becomes a single cell and gradually replaces the endothelial layer lining the smooth muscle of the spiral artery. Gradually, maternal blood penetrates from the mother's spiral artery into the interstitial space.[72] In this process, placental tissue produces a large amount of free radicals and generates oxidation. Intense stress occurs, but the placenta gradually adapts to this environment and returns to normal through appropriate antioxidant activity.[73,74] While physiological concentrations of endogenous glucocorticoids maintain fetal development, excess glucocorticoids *in utero* (i.e., maternal stress) adversely affect mammalian offspring primarily by "programming" abnormalities that occur after birth.[75] ROS are also thought to play a role in different phases of the endometrial cycle. The late luteal phase is characterized by high levels of lipid peroxide and a decrease in the antioxidant SOD. ROS affect PGF2α secretion through NF-κB activation.[76] Decreased estrogen and progesterone levels lead to decreased SOD expression and thus OS in the uterus, ultimately causing endometrial shedding and lack of implantation.

OS leads to endothelial cell dysfunction. Endothelial cell dysfunction in the uterus is the cause of many diseases. Moreover, there are many causes of endothelial cell dysfunction. TNF-α is known to cause endothelial cell damage, but the antioxidant cytokine Mn SOD neutralizes SO anions produced by TNF-α. This process is a self-defensive mechanism against TNF-α-induced OS. In addition, defective placentation causes placental hypoxia and ischemia-induced reperfusion injury, and the resulting OS triggers cytokine and PG release, leading to endothelial cell dysfunction and playing an important role in the development of preeclampsia.[77] Furthermore, ROS generated from NADP(H) oxidase are critical for vascular endothelial growth factor signaling *in vitro* and angiogenesis *in vivo*.[78] Endothelial NADP(H) oxidase activated by growth factors and cytokines produces ROS in a non-excessive amount. ROS produced in and around the vascular endothelium may play a role in normal cellular signaling mechanisms.

Preeclampsia is a vascular disorder of pregnancy, usually involving impaired placental development. Normotensive women also present with a complex multisystem disorder. OS increases nitration of p38 MAPK and consequently decreases its catalytic activity, which may cause the poor implantation and growth restriction observed in preeclampsia. Increased ROS concentrations in preeclampsia patients have been suggested by increased levels of MDA, a marker of lipid peroxidation.[79] Under normal conditions, the disruption of circulatory homeostasis is mainly due to vascular endothelial dysfunction in pre-eclampsia. It is characterized by a tendency to cause vasoconstriction and low anticoagulant activity. ROS appear to play a critical role in the endothelial dysfunction associated with preeclampsia. In other words, the pathological event in preeclampsia is OS-regulated vascular endothelial injury due to increased placental ROS or decreased antioxidant activity.[80]

Autoantibodies against the angiotensin receptor, AT1, particularly the second loop (AT1-AA), may stimulate NAD(P)H oxidase, leading to increased ROS production. In preeclamptic women, the AT1 receptor has been reported to increase both SO anion production and overexpression of NAD(P)H oxidase in cultured trophoblasts and smooth muscle cells. Thus, early placental development may be affected by dysregulated vascular development and function due to altered gene expression mediated by NAD(P)H oxidase.[81] Preeclamptic women produce excess ROS and show higher NAD(P)H expression than those without the pre-eclampsia. More specifically, women with early-onset pre-eclampsia have been reported to produce greater amounts of SO anions than women with late-onset disease. Affected women also have reduced TAS and placental GPx and low levels of vitamin C and E. Deficient vitamin C intake appears to be associated with an increased risk of pre-eclampsia and some studies have shown that pre-pregnancy multivitamin supplementation may reduce the risk of pre-eclampsia in normal or underweight women.[82]

CONCLUSION

OS affects the woman's entire reproductive system and process. Excessive production of ROS leads to OS events. ROS, including superoxide (O_2- -), H_2O_2 and hydroxyl (-OH), cause DNA damage, lipid peroxidation and protein damage. When mild OS, such as SOD and GPx, are formed, the antioxidant system starts to work. Moreover, when ROS levels exceed the scavenging capacity of the system, the redox system can also repair oxidized and damaged molecules using NADPH as the original electron source. Therefore, maintaining a high redox potential is an absolute precondition for maintaining reproductive systems in a healthy state.[10]

In this review, we mainly discussed the related reproductive diseases caused by OS and a series of signaling pathways, including PCOS, endometriosis, and preeclampsia. OS during

reproduction activates many molecules, but the interaction between them is not very clear, which requires us to identify signaling cues in other organs or other diseases. Compared to other diseases, research into diseases of the reproductive system is extremely complex, especially in both male and female infertility and pregnant women.

In this discussion, we summarized the following. First, OS plays a role in the development of reproductive system diseases, despite also being critical at low levels for normal fertility. Second, OS greatly disrupts reproductive organs, including the placenta. Third, the inflammatory environment caused by OS induces a series of signaling activations in the uterus.

Finally, by speculating on the relationship between these signaling molecules, we can re-examine future development trends in reproductive system diseases. In the future, a strategy to strengthen antioxidant systems and target mitochondria would be a big step. To increase the body's antioxidant capacity, ROS production from the mitochondrial ETC, which occurs in response to high glucose and fatty acid levels, should be reduced and also this reduction of ROS production should not significantly affecting ATP production.

Targeting mitochondria and increasing the overall antioxidant defense system may be critical. It is now well recognized that the pharmacological effects of antioxidants depend on their targeting. It is also known that it is beneficial to use classes of antioxidants separately from each other. Appropriately powered and well-designed randomized, placebo-controlled trials are needed to evaluate any evidence for the benefits or harm of a range of antioxidants at different concentrations and locations, or both.

Footnotes

Authorship Contributions

Surgical and Medical Practices: H.G., S.H.K., Concept: H.G., S.H.K., Design: H.G., S.H.K., Data Collection And Processing: H.G., S.H.K., Analysis And Interpretation: H.G., S.H.K., Literature Search: H.G., S.H.K., Writing: H.G., S.H.K.

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Original Article

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Validation of Pregnancy Unique Quantification of Emesis and Nausea (PUQE) Score in a Turkish Population

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ABSTRACT

Purpose: Nausea and vomiting of pregnancy (NVP) is a significant problem in the first trimester of pregnancy which may seriously affect quality of life. The Pregnancy Unique Quantification of Emesis and Nausea (PUQE) score is a useful tool to assess NVP severity. The aim of the study was to perform the Turkish validation of the PUQE scoring system.

Methods: A cross-sectional study was conducted in a single clinic between December 2023 and May 2025, involving pregnant women in their first trimester. The Turkish version of the PUQE questionnaire was developed using standardized translation and cultural adaptation guidelines. Participants completed the modified PUQE scale assessing nausea, vomiting, and retching over the past 24 hours. Statistical analyses included internal consistency (Cronbach's alpha), content validity, and correlation with clinical interventions (antiemetic and intravenous fluid use).

Results: Among 787 pregnant women enrolled, 40.7% reported symptoms of NVP. Participants with NVP had a significantly higher pre-pregnancy body mass index compared to those without NVP ($p=0.001$), while other demographic variables showed no significant differences. The Turkish version of the PUQE scale demonstrated excellent internal consistency (Cronbach's alpha =0.963). Corrected item-total correlations ranged from 0.81 to 0.91. PUQE scores were significantly associated with clinical intervention, including antiemetic use and intravenous fluid therapy ($p<0.001$), supporting the scale's clinical validity.

Conclusion: The PUQE scale was successfully adapted and validated in the Turkish language. Since PUQE is a three-item tool that is easy to apply and use, validation and adaptation to Turkish was helpful to evaluate the severity of NVP in any Turkish population.

Keywords: Hyperemesis gravidarum, nausea, vomiting, validation study

INTRODUCTION

Nausea and vomiting are common symptoms during pregnancy, typically beginning between the sixth and eighth weeks and often persisting until the sixteenth or even twentieth weeks.[1] These symptoms effect up to 70% of pregnant women, while the more serious form of nausea and vomiting of pregnancy (NVP), termed hyperemesis gravidarum (HG), is seen in 0.3-10.8% of pregnancies.[2] Diagnosis of HG is mostly based on clinical presentation, and persistence of NVP despite dietary modifications and antiemetic therapy is an important indicator supporting the diagnosis of the condition. The American College of Obstetricians and Gynecologists Practice Guideline advises that HG should be diagnosed when patients experience persistent vomiting without another identifiable cause, along with ketonuria, weight loss exceeding 5%, electrolyte imbalances, and abnormalities in thyroid and liver function tests.[3]

The etiopathogenesis of HG is multifactorial, and rapid increases in pregnancy-related hormones, such as human chorionic gonadotropin, estrogen, progesterone, placental growth hormone, prolactin, thyroxine, and adrenocortical

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hormones are thought to be responsible for nausea and vomiting.[4] In addition, elevated levels of ghrelin, leptin, nesfatin-1, and peptide YY have also been implicated in its pathogenesis.[5] In the United States, HG is the leading cause of hospitalization during the first 20 weeks of pregnancy and approximately 0.5% to 2.1% of affected patients require inpatient treatment.[4] HG is one of the most debilitating conditions affecting quality of life (QoL) during pregnancy and assessing the severity of the condition is a key factor in improving treatment effectiveness.

There are several questionnaires available for evaluating the severity of HG. For the assessment of nausea and vomiting, the rhodes index was initially developed for general clinical use and was later adapted for pregnancy in 2001.[6,7] However, its eight-item format may be difficult to complete in clinical settings, especially for patients experiencing severe symptoms. The absence of a validated tool specifically designed to assess the severity of HG contributed to the development of the Pregnancy Unique Quantification of Emesis and Nausea (PUQE) score as a standardized and clinically practical measure.

The PUQE score was first described in 2002 to assess the severity of HG. It is a three-item tool and evaluated symptoms over the last 12-hours.[8] Due to its ease of use in clinical practice and its utility in guiding treatment decisions, the PUQE score is considered a valuable tool. However, since the severity of nausea and vomiting symptoms can vary throughout the day and night, a 24-hour version of the PUQE score was developed in 2009 to improve accuracy.[9] There is also a modified PUQE score which evaluates the symptoms for the entire first trimester.[10] This questionnaire consists of three items designed to assess the severity of symptoms. The Royal College of Obstetricians and Gynaecologists guideline recommend that clinical management and treatment decisions should be guided by the PUQE score-based classification system.[11]

Accurate and reliable tools, validated in Turkish, will be necessary for assessing the severity of HG in any Turkish population of pregnant women. This will provide accurate clinical evaluation and lead to better treatment decisions. Therefore, the aim of the present study was to perform the Turkish validation of the PUQE scoring system.

METHODS

A cross-sectional study was conducted prospectively between December 1, 2023 and May 15, 2025 in a single private clinic. All women attending in he first trimester were eligible for inclusion. The study was conducted in accordance with Declaration of Helsinki and approved by the University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital Ethics Committee with (approval number: KAEK/11.10.2023.481, date: 23.10.2023). All women gave informed consent orally before participation.

We adapted the modified PUQE questionnaire, which evaluated three specific symptoms of NVP for the last 24 hours.[9] The questionnaire was applied to the patients by nurses in the outpatient clinic. The Turkish version of PUQE score was paper-based, and the average time to complete was only two minutes. PUQE score uses a five-point Likert scale that measures the duration of nausea, frequency of vomiting, and the frequency of retching or dry heaves in the last 24 hours. Scores were calculated by assigning a value to each response from “causing no discomfort” (score of 1) to “causing the most possible discomfort” (score of 5). The total score was calculated by summing the responses to each of the three items, which ranged from no symptoms (score of 3) to maximal symptoms (score of 15). This total was used to define mild NVP (score of 3-6), moderate NVP (score of 7-12), and severe NVP (score of ≥13).

The recommendations of the translation and cultural adaptation group and the consensus based standards for the selection of health measurements checklist were followed for the cross-cultural adaptation and validation of the Turkish version of the PUQE questionnaire.[12,13] The questionnaire was translated into Turkish by consensus of two experts with medical background (Appendix 1).

Pregnant women’s demographic data was collected including the current pregnancy, obstetric and medical history, lifestyle and treatments for NVP. All data was secured in SPSS database. SPSS version 22.0 (IBM Corporation, Armonk, NY, USA) was used to conduct the statistical analysis. The test for normal distribution was conducted using the Kolmogorov-Smirnov test. For continuous variables having a normal distribution, descriptive statistics are displayed as mean ± standard deviation (SD). Fisher’s exact test or the chi-squared test was used to compare categorical variables. The independent samples t-test was used to compare continuous variables that were regularly distributed. For all tests, a p -value of less than 0.05 was considered statistically significant.

Statistical Analysis

Content validity, which reflects whether the questionnaire is meaningful and appropriate for patients, was assessed by an expert committee of two obstetricians and gynecologists. Each item was rated on a 4-point scale (1= not acceptable, 2= poorly acceptable, 3= acceptable, 4= strongly acceptable). The content validity ratio (CVR) was calculated using Lawshe’s method but, because CVR values are not considered reliable with fewer than five experts, the results were interpreted with caution. The content validity index (CVI) was calculated at both the item level (I-CVI) and the scale level (S-CVI/Ave), based on the proportion of items rated 3 or 4. Full agreement (I-CVI =1.0) was required with two experts for an item to be considered valid. Internal consistency assessed using Cronbach’s alpha analysis, with values between 0.70 and 0.99 indicating good internal consistency. Criterion validity was assessed by Pearson’s correlation test, comparing nausea and vomiting severity scores with clinical parameters including the need for antiemetic medication and intravenous fluid transfusion.

RESULTS

Of the 912 cases admitted during their first trimester of pregnancy, 11 were excluded because of ectopic pregnancy, 14 cases did not report or fill the PUQE questionnaire, 73 patients were diagnosed to have empty gestational sac, or no

embryonic or fetal heart beat by the end of 14 weeks, and 27 cases could not speak or read Turkish. This resulted in a total of 787 pregnant women in the first trimester being enrolled in the study.

Among the 787 pregnant women enrolled in the study, 321 (40.7%) reported having mild (n=186, 23.6%), moderate (n=122, 15.5%) or severe (n=13, 1.7%) NVP, while 466 women (59.2%) had none of the symptoms. Primigravid women constituted 39.7% (n=313) of the study group. Regular antiemetic use was mandatory in 66 (8.4%) women while 26 (3.3%) women needed regular intravenous fluid infusions. The demographic data according to presence and absence of NVP is presented in Table 1. Age, working status, nulliparity, multiple pregnancy rate, tobacco use during pregnancy, diabetes and hypertension rates were statistically similar between the NVP and non-NVP groups ($p>0.05$). Mean pre-pregnancy body mass index (BMI) was 27.8±6.3 in the non-NVP group and 29.2±5.8 in NVP group($p=0.001$). In terms of education, the non-NVP group contained a significantly larger proportion of illiterate women ($p=0.005$).

The demographic data according to the severity of PUQE score is presented in Table 2. Age, pre-pregnancy BMI, education status, working status, nulliparity, multiple pregnancy rate, tobacco use during pregnancy, diabetes and hypertension rates were statistically similar between mild, moderate and severe NVP groups ($p>0.05$).

Table 1. The demographic data according to presence and absence of nausea and vomiting of pregnancy

Variable	Patients without NVP (n=466)	Patients with NVP (n=321)	*p* value
Age (years)	27.8±6.3	29.2±5.8	0.2
Pre-pregnancy body mass index (kg/m^2)	27.8±6.3	29.2±5.8	0.001*
Education			
Illiterate	73 (18.3)	23 (8.8)	0.005**
Primary school	45 (11.3)	26 (10)	
Secondary school	74 (18.5)	60 (23)	
High school	157 (39.3)	128 (49)	
University	50 (12.5)	24 (9.2)	
Working	96 (20.6)	79 (24.6)	0.1
Nulliparity	197 (42.3)	116 (36.1)	0.08
Twin	23 (4.9)	19 (5.9)	0.5
Tobacco use during pregnancy	39 (8.4)	39 (12.1)	0.08
Diabetes	13 (2.7)	12 (3.7)	0.5
Hypertension	7 (1.5)	9 (2.8)	0.2

*Statistically significant ($p<0.05$), Students t-test, ** Statistically significant ($p<0.05$), chi-square test
NVP: Nausea and vomiting of pregnancy

Table 2. The demographic data according to the severity of PUQE score among women with nausea and vomiting of pregnancy

Variable	Mild (n=186)	Moderate (n=122)	Severe (n=13)	*p* value
Age (years)	29.7±5.9	28.7±5.8	28.1±3.6	0.2
Pre-pregnancy body mass index (kg/m^2)	28.8±4.4	29.4±4.5	31.1±4.2	0.1
Education				
Illiterate	15 (10.5)	7 (6.6)	1 (8.3)	0.4
Primary school	15 (10.5)	10 (8.1)	1 (8.3)	
Secondary school	28 (19.6)	31 (29.2)	1 (8.3)	
High school	72 (50.3)	47 (44.3)	9 (75)	
University	13 (9.1)	11 (10.4)	0	
Working	13 (9.1)	4 (3.7)	0	0.7
Nulliparity	65 (34.9)	44 (36.1)	7 (53.8)	0.3
Twin	10 (5.4)	8 (6.6)	1 (7.7)	0.8
Tobacco use during pregnancy	22 (11.8)	16 (13.1)	1 (7.7)	0.8
Diabetes	3 (1.6)	9 (7.3)	0	0.1
Hypertension	6 (3.2)	3 (2.4)	0	0.7

PUQE: Pregnancy Unique Quantification of Emesis and Nausea

Item pool, retention and decisions based on reliability analysis is presented in Table 3. The item means ranged from 0.8 to 1, indicating a moderate distribution of responses across items. SDs were within an acceptable range, suggesting variability in participant responses. The corrected item-total correlation coefficients ranged between 0.81 and 0.91, well above the acceptable threshold of 0.30. These values indicate that each item demonstrates strong discrimination and contributes significantly to the overall construct of nausea and vomiting severity. The overall PUQE score in the 787 pregnant women had a Cronbach's alpha coefficient of 0.963 and a mean score of 4.6±2.68 (3-15) demonstrating good internal reliability. Based on these results, all items were retained in the final version of the Turkish PUQE scale.

Correlation analysis of PUQE score items with each other and with antiemetic use or intravenous fluid infusion is given in Table 4. The number of participants included in the correlation analysis was 787. All three PUQE items showed significant positive correlations with one another (r=0.656-0.800, $p<0.001$), indicating internal coherence among the items measuring nausea, vomiting, and retching. In addition, each item was positively correlated with the use of antiemetic medications and intravenous fluid therapy. The strongest correlations were observed between vomiting and antiemetic use (r=0.701, $p<0.001$), supporting the clinical relevance of the scale. These findings suggest that higher scores on the PUQE items are associated with increased clinical intervention, consistent with a higher severity of symptoms.

DISCUSSION

In this study, we aimed to translate into Turkish and then evaluate the validity and reliability of the Turkish version of

Table 3. Item pool, retention and decisions based on reliability analysis

PUQE item no	Item mean	Item standard deviation	Corrected item total correlation	Cronbach's alpha
1	1	1.5	0.91	0.89
2	0.8	1.2	0.81	0.76
3	0.9	1.4	0.87	0.84

PUQE: Pregnancy Unique Quantification of Emesis and Nausea

Table 4. Correlation analysis of PUQE score items with each other and with antiemetic use or intravenous fluid infusion

Correlations						
For all correlations n=787		**Item 1**	**Item 2**	**Item 3**	**Antiemetic**	**4 fluids**
Item 1	Pearson correlation	1	0.721**	0.800**	0.568**	0.404**
	Sig. (2-tailed)		<0.001	<0.001	<0.001	<0.001
	n	787	787	787	787	787
Item 2	Pearson correlation	0.721**	1	0.656**	0.701**	0.529**
	Sig. (2-tailed)	<0.001		<0.001	<0.001	<0.001
	n	787	787	787	787	787
Item 3	Pearson correlation	0.800**	0.656**	1	0.474**	0.345**
	Sig. (2-tailed)	<0.001	<0.001		<0.001	<0.001
	n	787	787	787	787	787
Antiemetic	Pearson correlation	0.568**	0.701**	0.474**	1	0.611**
	Sig. (2-tailed)	<0.001	<0.001	<0.001		<0.001
	n	787	787	787	787	787
4 fluids	Pearson correlation	0.404**	0.529**	0.345**	0.611**	1
	Sig. (2-tailed)	<0.001	<0.001	<0.001	<0.001	
	n	787	787	787	787	787

**Correlation is significant at the 0.01 level (2-tailed)
PUQE: Pregnancy Unique Quantification of Emesis and Nausea

the 24-hour PUQE scale in a large cohort of pregnant women. The Turkish PUQE score demonstrated excellent internal consistency, with a Cronbach's alpha of 0.963, indicating that the items reliably measure the underlying construct of NVP. Corrected item-total correlations ranged from 0.81 to 0.91 as seen in Table 3, further supporting the contribution of each item to the overall score. Moreover, the three core items of the PUQE scale showed strong and significant inter-item correlation, suggesting high internal coherence. The observed associations between higher PUQE item scores and increased use of antiemetic medication and/or intravenous fluid therapy provide additional evidence for the clinical validity of the scale (Table 4). These results collectively support the Turkish PUQE as a psychometrically sound instrument for quantifying the severity of NVP in pregnant women.

There are some studies assessing a PUQE score with language translation, however, only a few studies cross-culturally adapted and validated the PUQE score. For instance, the Norwegian PUQE-24 (Svangerskaps Utløst Kvalme Kvantifisering-SUKK) was prospectively validated among women with HG and healthy pregnant controls.[14] PUQE scores distinguished severe cases (median 13 vs. 7) and correlated inversely with nutritional intake ($r=-0.5$, $p<0.001$). This study involved 31 healthy pregnant women and 38 HG patients who were hospitalized. PUQE scores were obtained before and after treatment. Thus the Norwegian study differs from ours as it evaluated before and after treatment PUQE scores in a cohort of hospitalized HG patients. To date, the Turkish study of the PUQE-24 has been one of the few linguistically and psychometrically validated adaptations of the PUQE score.[15] In this study the scale underwent a rigorous translation, cross-cultural adaptation, and validation process. The authors reported acceptable internal consistency (Cronbach's alpha =0.75) and strong item-total correlations (r=0.75-0.85). However, it is important to note that this study involved 90 patients and any of them reported severe NVP which PUQE score was 13-15. In addition, the study patients self-reported NVP. However, antiemetic use or intravenous treatment and correlation with PUQE score was not assessed, unlike in the present study. There is a French validation study of the PUQE score which included 399 patients and 238 of them reported NVP.[16] This study suggested that total PUQE score and self-reported NVP symptoms and NVP-QoL score were positively correlated. However, correlation analysis of PUQE score items with each other was not applied, again differing from the present study. A study conducted in Finland investigated the usability PUQE score in hospitalized HG patients compared to the visual analog score and NVP-QoL.[17] Although this was not a validation and cultural adaptation study, it is valuable that they showed the positive correlation between PUQE score and severity of NVP.

PUQE score is a handy tool to assess the severity of HG since it is quick t complete and self-reported. Although it is mostly used to assess the severity of NVP in outpatient clinic, there are some studies that have shown that PUQE score before and after hospitalization demonstrated a reliable change with changes in symptoms.[14,17-19] The original studies both assessing the symptoms for 12 hours, 24 hours and the entire first trimester with PUQE questionnaire showed a significant correlation between the PUQE score and symptom severity.[8-10]

The strengths of our study include the large cohort, including both NVP and non-NVP patients which provides an advantage in terms of testing the discriminatory power of the questionnaire. Comparing the mild, moderate and severe NVP patients is also increases the power of the study.

Study Limitations

Limitations of the study include the single-center design. In addition, NVP severity was self-reported rather than assessed using another validated tool. PUQE score was not correlated with another validated NVP assessment tool. Lastly, patients were not reassessed with the Turkish PUQE scale after treatment.

CONCLUSION

Since PUQE score is a three-item tool with ease of use, validation and adaptation to Turkish is important to evaluate the severity of NVP in Turkish populations. It will also aid in treatment decision and assessing response to treatment in any Turkish population. This tool can now be used in both clinical and research settings in Turkey but there should be multi-center studies with large patient groups to compare the PUQE score with other NVP questionnaires to confirm its validity and reliability in the Turkish language.

Ethics

Ethics Committee Approval: The study was conducted in accordance with Declaration of Helsinki and approved by the University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital Ethics Committee with (approval number: KAEK/11.10.2023.481, date: 23.10.2023).

Informed Consent: All women gave informed consent orally before participation.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.H.C., E.A., Concept: E.H.C., Design: R.A.B., E.A., B.Y., Data Collection or Processing: E.H.C., E.A., Analysis or Interpretation: B.Y., Literature Search: R.A.B., B.Y., Writing: R.A.B.

Conflict of Interest: No conflict of interest was declared by the authors.

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Appendix 1: Translation of the PUQE score in Turkish

PUQE (gebeliğe özgü bulantı ve kusma puanlaması) **Lütfen size en uygun cevabı işaretleyiniz.**				
1. Son 24 saat içinde ne kadar süre bulantı veya mide rahatsızlığı hissettiniz?				
Hiç (1)	1 saat veya daha az (2)	2-3 saat (3)	4-6 saat (4)	6 saatten daha fazla (5)
2. Son 24 saat içinde kustunuz mu, kusmuk çıkardınız mı?				
Hiç kusmadım (1)	1-2 kez kustum (2)	3-4 kez kustum (3)	5-6 kez kustum (4)	7 ve daha fazla kustum (5)
3. Son 24 saat içinde kaç kez midenizden bir şey çıkmadan öğürdünüz veya geğirdiniz?				
Hiçbir zaman (1)	1-2 kez (2)	3-4 kez (3)	5-6 kez (4)	7 kez ve daha fazla (5)
Parantez içindeki sayıları toplayarak PUQE-24 skorunu hesaplayınız: Hafif 4-6 Orta: 7-12 Ağır: ≥13				
PUQE: Pregnancy Unique Quantification of Emesis and Nausea				

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Perinatal Outcomes in HIV-Positive Pregnant Women: A Multicentric Study

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ABSTRACT

Purpose: To evaluate perinatal outcomes and maternal human immunodeficiency virus (HIV) disease progression in pregnant women

Methods: Retrospective multicentric review of a cohort of 34 HIV-positive pregnant women delivering at four Turkish hospitals (2009-2021). Data included obstetric/neonatal parameters and serial laboratory values.

Results: Mean maternal age was 30.8±3.3 years and 52.9% were diagnosed during pregnancy. HIV viral load remained suppressed [median 254 copies/mL interquartile range (IQR: 50-1200) in first trimester and 211 copies/mL (IQR: 40-900) at delivery]. Mean birth weight was 2351.8±727.0 g. Pregnancy complications included premature rupture of membranes (29.4%), preterm labor (23.5%), and placental abruption (5.9%). Among 32 infants followed-up, none acquired HIV (0% mother-to-child transmission but two lost to follow-up). No maternal disease progression occurred.

Conclusion: Antiretroviral therapy and cesarean delivery resulted in 0% mother-to-child HIV transmission in tested infants in this cohort. High obstetric complication rates and frequent late diagnosis underscored the need for enhanced prenatal screening and individualized delivery planning. Neonatal outcome data were limited to parameters with complete and consistent documentation.

Keywords: HIV, pregnancy, perinatal outcomes, antiretroviral therapy, maternal health, neonatal health

INTRODUCTION

Global human immunodeficiency virus (HIV) prevalence remains significant, with approximately 39 million affected individuals in 2024.[1] In Türkiye, HIV incidence has risen steadily, with an estimated 32,000 current cases.[2] Antiretroviral therapy (ART) has transformed HIV into a chronic condition, increasing pregnancies among HIV-positive women.[3] While ART reduces mother-to-child transmission (MTCT) to less than 2% in high-resource settings,[4] pregnancy complications remain poorly characterized in Turkish cohorts. This study evaluated perinatal outcomes and HIV progression in pregnant Turkish women receiving ART.

METHODS

Study Design and Population

A retrospective cohort study was conducted, including all HIV-positive pregnant women who delivered at four referral hospitals in Türkiye between August 2009 and January 2021. Inclusion criteria were: singleton pregnancy; delivery at or beyond 20 weeks of gestation; and confirmed HIV diagnosis. Exclusion criteria were: incomplete ART adherence; chronic hepatitis B virus or hepatitis C virus coinfection, major pre-existing conditions such as diabetes mellitus or renal insufficiency; and early pregnancy loss (<20 weeks). All hospitals adhered

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to the same national HIV treatment protocols throughout the study period, which helped minimize inter-center variability and ensured consistency in patient care. The study was approved by Selçuk University Local Ethics Committee (No: 2021/54, dated: 10.02.2021) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Clinical Protocols

All participating centers followed standardized national protocols for prevention of MTCT (PMTCT) of HIV, which included:

- Maternal combination ART consisting of nucleoside reverse transcriptase inhibitors + protease inhibitor
- Elective cesarean delivery scheduled at 38 weeks of gestation
- Intrapartum intravenous zidovudine (ZDV) until cord clamping
- Neonatal nevirapine prophylaxis for 12 weeks
- Exclusive formula feeding

Data Collection

Data were extracted from medical records and included:

- Maternal characteristics: age, gravidity, parity, gestational age at delivery, mode of delivery, comorbidities, timing of HIV diagnosis, ART regimen and duration, and pregnancy complications [gestational diabetes, hypertensive disorders, preterm labor, premature rupture of membranes (PROM), placental abruption].
- Neonatal parameters: birth weight, Apgar scores at 1 and 5 minutes, and HIV status (determined by PCR at 18 months of age).
- Laboratory findings: HIV viral load (copies/mL), CD4+ T-lymphocyte count (cells/μL), hemoglobin (g/dL), white blood cell count (x10^3/L), and platelet count (x10^3/L) measured during the first trimester and at delivery.
- Maternal disease progression was defined as a ≥25% decline in CD4+ count from baseline, development of an opportunistic infection, or worsening of World Health Organization (WHO) clinical staging during pregnancy or within six weeks postpartum.

Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS), version 21.0 (IBM Corp., Armonk, NY, USA). Normality of continuous variables was assessed using the Kolmogorov-Smirnov test. Normally distributed continuous variables are expressed as mean ± standard deviation, non-normally distributed variables as median [interquartile range, (IQR)], and categorical variables as frequencies and percentages. Changes in laboratory parameters between the first trimester and delivery were analyzed using paired t-tests (normally distributed) or Wilcoxon signed-rank tests (non-normally distributed). A p-value <0.05 was considered statistically significant.

RESULTS

Cohort Characteristics

Thirty-four HIV-positive pregnant women were included. The mean maternal age was 30.8±3.3 years. Most women were married (70.6%) and 52.9% were employed. Low socioeconomic status was reported in 47.1% of cases, and 41.2% smoked during pregnancy. Regarding HIV diagnosis, 52.9% were diagnosed during the current pregnancy, 23.5% were aware of their status before conception, and the remaining 23.6% were diagnosed at delivery or had undocumented timing. All women were classified as WHO stage 1 at enrollment (Table 1).

Laboratory Findings

Median HIV viral load was 254 copies/mL (IQR: 50-1200) in the first trimester and 211 copies/mL (IQR: 40-900) at delivery (p=0.08). Median CD4+ count at delivery was 512 cells/μL (IQR: 320-780). Significant hematological changes were observed from the first trimester to delivery: white blood cell count increased from 5382.4±2727.2 to 8223.5±3885.0 x10^3/L (p<0.01), hemoglobin decreased from 9.8±1.2 to 8.7±1.3 g/dL (p<0.01), and platelet count decreased from 220,411.8±56,265.7 to 204,353.0±54,586.0 x10^3/L (p=0.03) (Table 2).

Obstetric and Neonatal Outcomes

All women delivered by cesarean section at a mean gestational age of 35.4±2.1 weeks. The mean birth weight was 2351.8±727.0 g. Median Apgar scores were 7 (range: 5-9) at 1 minute and 8 (range: 5-10) at 5 minutes. Pregnancy complications occurred in 58.8% of women, including PROM (29.4%), preterm labor (23.5%), and placental abruption (5.9%). No cases of gestational diabetes or hypertensive disorders were reported. Among 34 newborns, 32 (94.1%) were tested for HIV at 18 months and all were negative. Two infants (5.9%) were lost to follow-up before HIV status could be confirmed (Table 3).

DISCUSSION

This multicentric study from Türkiye demonstrates two key findings: (1) a 0% MTCT rate among infants with confirmed maternal HIV status, achieved through combination ART and cesarean delivery; and (2) high rates of pregnancy complications, particularly PROM (29.4%) and preterm labor (23.5%). Although the overall transmission rate appears to be 5.9%, this is due to two cases lost to follow-up. Among the 32 tested infants, the MTCT rate was 0%, consistent with international benchmarks.

The absence of MTCT in the 32 tested infants aligns with global benchmarks for PMTCT success in settings with comprehensive ART programs.[4,5] Our findings support the effectiveness of the Turkish national PMTCT protocol, which includes combination ART, elective cesarean delivery, intrapartum ZDV, and infant nevirapine prophylaxis. However, the universal use of cesarean delivery in our cohort, despite all

Table 1. Maternal characteristics of HIV-positive pregnant women (n=34)		
Parameter	**Value**	**Percentage (%)**
Demographic characteristics		
Age [years, mean ± SD (range)]	30.8±3.3 (25-37)	-
Gravida [median (range)]	2 (1-5)	-
Parity [median (range)]	1 (0-4)	-
Marital status, n (%)		
Single	8	23.5
Married	24	70.6
Other	2	5.9
Educational status, n (%)		
Illiterate	12	35.3
Primary education	12	35.3
High school	6	17.6
Higher education	4	11.8
Occupation, n (%)		
Employed	18	52.9
Unemployed	16	47.1
Socioeconomic status, n (%)		
Low	16	47.1
Medium	14	41.2
High	4	11.8
Ethnicity, n (%)		
Turkish	16	47.1
Asian	10	29.4
African	6	17.6
European	2	5.9
Clinical characteristics		
Smoking, n (%)		
No	20	58.8
Yes	14	41.2
Alcohol use, n (%)		
No	18	52.9
Yes	16	47.1
HIV diagnosis, n (%)		
Before conception	8	23.5
During pregnancy	18	52.9
At birth	8	23.5
Other STDs, n (%)		
No	28	82.4
Syphilis	6	17.6
Antiretroviral therapy status, n (%)		
Started before pregnancy	14	41.2
Started during pregnancy	20	58.8
Never	0	0.0

Data are presented as mean ± standard deviation (range), median (range), or n (%)
Syphilis was the only reported STD in this study
STDs: Sexually transmitted diseases, HIV: Human immunodeficiency virus, SD: Standard deviation

Table 2. Hematological parameters in HIV-positive pregnant women

Parameter	First trimester	Birth	*p*-value*
HIV viral load (copies/mL), median [IQR]	254 (50-1200)	211 (40-900)	0.08
HIV viral load distribution, n (%)			
≤1000	30 (88.2%)	34 (100.0%)	0.04**
>1000	4 (11.8%)	0 (0.0%)	
CD4+ (cells/μL), mean ± SD	410.0±161.6	456.2±208.0	0.12
CD4+ distribution, n (%)			
≤200	4 (11.8%)	6 (17.6%)	0.50**
>200	30 (88.2%)	28 (82.4%)	
CD8+ (cells/μL), mean ± SD	553.6±199.5	550.0±177.8	0.89
CD4+/CD8+ Ratio, mean ± SD	0.80±0.2	0.86±0.4	0.34
WBC (x10⁹/L), mean ± SD	5382.4±2727.2	8223.5±3885.0	<0.01
Hemoglobin (g/dL), mean ± SD	9.8±1.2	8.7±1.3	<0.01
Platelets (x10⁹/L), mean ± SD	220411.8±56265.7	204353.0±54586.0	0.03

*Wilcoxon signed-rank test for continuous variables, **McNemar test for categorical variables
Data are presented as mean ± standard deviation, median [interquartile range], or n (%)
IQR: Interquartile range, SD: Standard deviation, HIV: Human immunodeficiency virus, WBC: White blood cell

Table 3. Obstetric and neonatal outcomes in HIV-positive pregnant women (n=34)

Parameter	Value	Percentage (%)
WHO HIV stage, n (%)		
Stage 1	34	100.0
Antiretroviral therapy (ART), n (%)		
Yes	34	100.0
No	0	0.0
Mode of delivery, n (%)		
Vaginal	0	0.0
Cesarean	34	100.0
Fetal characteristics		
Gestational age (weeks, mean ± SD)	35.4±2.1	-
Birth weight (g, mean ± SD)	2351.8±727.0	-
Apgar score, 1st minute [median (range)]	7 (5-9)	-
Apgar score, 5th minute [median (range)]	8 (5-10)	-
Congenital anomalies, n (%)		
No	34	100.0
Yes	0	0.0
Pregnancy complications, n (%)		
Premature rupture of membranes	10	29.4
Placental abruption	2	5.9
Preterm labor	8	23.5
None	14	41.2
Neonatal HIV diagnosis, n (%)		
No	32	94.1
Yes	2	5.9

Data are presented as mean ± standard deviation, median [range], or n (%)
HIV: Human immunodeficiency virus, SD: Standard deviation, WHO: World Health Organization

women achieving viral suppression (viral load ≤1000 copies/mL) by delivery, warrants scrutiny. Current WHO guidelines support vaginal delivery for women with viral loads below 1000 copies/mL,[6] and a shift toward individualized delivery planning could reduce surgical risks without compromising MTCT prevention.

The high rates of PROM and preterm labor observed in the present study exceed those reported in the general Turkish pregnant population (PROM: 10-12%; preterm labor: 10-15%).[7] These complications may be multifactorial, involving HIV-associated immune dysregulation, ART effects, and high rates of modifiable risk factors, such as smoking (41.2%) and low socioeconomic status (47.1%).[8] The absence of gestational diabetes and hypertensive disorders contrasts with some studies,[9] possibly due to our small sample size or population-specific factors.

Late diagnosis of HIV, with more than half of diagnoses made during the pregnancy studied, remains a critical concern, limiting opportunities for preconception ART optimization. This finding is consistent with reports from other settings[10] and underscores the need for enhanced prenatal HIV screening programs.

Study Limitations

Our study has several limitations: (1) the small sample size (n=34) reflects the low prevalence of HIV in Turkish pregnant women but limits statistical power; (2) the absence of an HIV-negative control group restricts direct comparisons of complication rates; (3) neonatal outcomes such as neonatal intensive care unit admission and congenital anomalies were inconsistently documented and could not be analyzed; (4) the retrospective design introduces potential biases in data collection; and (5) the 11-year study period may encompass evolving clinical practices, although standardized national protocols minimized variability.

CONCLUSION

Effective ART and obstetric management, including cesarean delivery, achieved low MTCT rates in HIV-positive pregnancies. However, high rates of pregnancy complications and late HIV diagnoses underscore the need for enhanced prenatal screening and vigilant obstetric care. Enhanced preconception screening programs and early diagnosis will be important for timely initiation of ART and improved perinatal outcomes. While our findings suggest that ART and cesarean delivery are associated with low perinatal transmission rates, these results should be interpreted cautiously given the lack of a control group. Future research should focus on optimizing delivery methods based on viral load and evaluating long-term outcomes.

Ethics

Ethics Committee Approval: The study was approved by Selçuk University Local Ethics Committee (no: 2021/54, dated: 10.02.2021).

Informed Consent: Written informed consent was obtained from all participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: N.G.K, A.B., M.K., Concept: N.G.K, F.A., M.K., Design: N.G.K, Ç.Ç., A.K.Ü., M.K., Data Collection or Processing: N.G.K, A.B., F.A., Ç.Ç., A.K.Ü., S.S., N.Ş., Ç.Ç., M.K., Analysis or Interpretation: N.G.K, S.S., M.K., Literature Search: N.G.K, N.Ş., Ç.Ç., M.K., Writing: N.G.K, M.K.

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Original Article

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Prevalence and Characteristics of Pelvic Congestion Syndrome in Infertile Women: A Cross-Sectional Study

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ABSTRACT

Purpose: Pelvic congestion syndrome (PCS) is a complex condition characterized by chronic pelvic pain (CPP) resulting from engorgement and dilatation of pelvic veins. Although PCS is primarily associated with CPP, recent research suggests a potential link between PCS and fertility problems. The aim of this cross-sectional study was to determine the prevalence of PCS in a large cohort of infertile women, and to identify and analyze associated demographic, clinical and ultrasound characteristics.

Methods: The study included 1,343 women presenting to a single infertility clinic. Participants underwent demographic interviews, gynecological examination, endocrinological workup, and transvaginal examination. Color Doppler identified veins, arteries and flow velocity during the val-salva maneuver. Patients with any ovarian vein with a diameter >5 mm, retrograde ovarian flow, >4 pelvic veins >4 mm diameter, or dilated arcuate veins communicating between bilateral pelvic varicose veins were diagnosed as PCS.

Results: Ultrasonographic evaluation identified a 5% prevalence (n=67) of PCS in this cohort. Women with PCS exhibited significantly lower rates of prior pregnancies (4.5% vs. 21.2%; $p=0.001$) and lower mean total antral follicle count (9.3+/-4.4 vs. 12.9+/-5.8; $p<0.001$) compared to infertile women without PCS. None of the women with PCS had polycystic ovary syndrome (PCOS) (0% vs. 17.3%; $p<0.001$). Symptoms such as CPP ($p<0.001$), hemorrhoids ($p<0.001$), dyspareunia ($p<0.001$), dysmenorrhea ($p<0.001$), lower extremity varices ($p=0.009$ for left; $p<0.001$ for right), vulvar varices ($p=0.002$) and hematuria ($p=0.01$) were significantly more prevalent in PCS group.

Conclusion: This large prospective cohort of 1,343 infertile women revealed a 5% prevalence of PCS using strict sonographic criteria. This finding is clinically significant, suggesting PCS as a previously omitted factor in 1 of 20 infertility cases. The findings found no evidence of PCS co-existence with PCOS and significant differences between groups in terms of frequency of a range of symptoms including CPP, dyspareunia, dysmenorrhea, and varices. These results suggest PCS may have a role in primary infertility and altered ovarian function.

Keywords: Pelvic pain, venous insufficiency, infertility, prevalence, ultrasonography

INTRODUCTION

Pelvic congestion syndrome (PCS) is a complex condition involving chronic pelvic pain (CPP) due to engorgement and dilation of the pelvic veins, particularly the ovarian and internal iliac veins. PCS generally results from valvular insufficiency, which is characterized by the failure of the one-way venous valves. This results in retrograde blood flow and accumulation. PCS may also result from venous obstruction.[1,2] The etiology of PCS is multifactorial, involving a combination of predisposing factors. Hormonal influences, such as elevated estrogen levels, are thought to contribute by weakening the walls of pelvic veins, making them more susceptible to dilation.[3]

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Genetic predisposition and anatomical abnormalities, such as "nutcracker syndrome" which is the compression of the left renal vein or iliac vein, can also contribute to the development of PCS.[4] The reported prevalence of PCS varies across different populations. CPP is responsible for approximately 10% to 20% of gynecological visits, with its global prevalence estimated to be between 6% and 27%. PCS may account for CPP in up to 30% of women affected by this condition.[5-7]

While PCS is primarily recognized for its association with CPP, emerging research suggests a potential, though not yet fully elucidated, link between PCS and fertility impairment.[8,9] There are a few case series and reports of pregnancies after treatment in the literature that may suggest a possible link between PCS and infertility. However, this issue has not been proven etiologically, nor has causality been demonstrated in appropriately designed studies. Furthermore, there is a scarcity of large-scale studies specifically quantifying the prevalence of PCS within infertile populations and comprehensively characterizing the associated demographic, clinical, and sonographic features in this specific cohort.

The current study was undertaken to address this specific knowledge gap and provide a clearer understanding of the role of PCS in female infertility. The objective of this study was to determine the prevalence of PCS in a large cohort of infertile women presenting to a single infertility clinic and to identify and analyze the associated demographic, clinical, and ultrasound characteristics of these women compared to infertile women without PCS.

Diagnosing PCS can be challenging due to the non-specific and overlapping nature of its symptoms with numerous other gynecological and non-gynecological conditions. A thorough medical history and physical examination are essential initial steps, followed by imaging modalities such as venography as a gold standard.[5] Ultrasonography is a primary non-invasive tool for visualizing pelvic veins and identifying varicosities or abnormalities.[10] In the current study, PCS was diagnosed based on specific ultrasonographic criteria, consistent with established guidelines.[1]

METHODS

Ethics approval had been obtained from Tekirdağ Namık Kemal University Ethics Committee (approval number: 2024.52.03.16, date: 26.03.2024). Between May 2024 and May 2025, all consecutive women presenting to a single infertility clinic for evaluation were screened for eligibility. A total of 1,343 women who met the inclusion criteria and provided informed consent were prospectively enrolled in this prospectively collected cross-sectional study. All assessments were performed by a single in vitro fertilization specialist with more than 25 years of experience in gynecological ultrasonography. All menstruating women aged between 18 and 45 years and diagnosed with primary or secondary infertility were included in the study. The exclusion criteria were: being menopausal; being diagnosed with pelvic inflammatory disease during the examination; having a history of major pelvic surgery, including oophorectomy or deep endometriosis surgery; and being diagnosed with a gynecological malignancy. All women were interviewed for demographic variables, urogynecological and pelvic pain symptomatology. A through gynecological examination and endocrinological work up of patients was followed by transvaginal examination. Presence of any vulvar and lower extremity varices were recorded. A voluson E8 expert system with a 2-10 MHz transvaginal probe was used for gynecological ultrasound examination. If ovarian veins could not be identified during transvaginal examination, transabdominal pelvic ultrasonography using 2-8 MHz curved transducer was conducted with patient in 45 degrees supine position or in left or right lateral decubitus position, especially in obese women. Subsequently color doppler was used to identify the veins, arteries and flow velocity waveforms during the val-salva maneuver. PCS was diagnosed in the presence of one of the following criteria: ovarian vein diameter more than 5 mm; retrograde flow in an ovarian vein; more than four pelvic veins greater than 4 mm in diameter; and/or dilated arcuate veins in the myometrium communicating between bilateral pelvic varicose veins.[1] The normal diameter of pelvic veins was accepted to be less than or equal to 4 mm in diameter. The endometriosis group, one of the gynecologic pathologies investigated for co-existence with PCS in the study, was composed of patients with endometrioma observed by ultrasonography and patients who had undergone surgery and received this diagnosis. The hydrosalpinx group consisted of patients diagnosed by hysterosalpingography and the leiomyoma group consisted of patients diagnosed by ultrasonography. The Rotterdam criteria were used to diagnose polycystic ovarian syndrome (PCOS). Patients were identified as having PCOS if they presented with at least two of the following three features: (1) oligo and/or anovulation; (2) clinical and/or biochemical signs of hyperandrogenism; and (3) polycystic ovaries as seen on ultrasound, characterized by 12 or more follicles measuring 2-9 mm in diameter and/or an ovarian volume exceeding 10 cm^3.[11]

Statistical Analysis

The data collected through the questionnaires and patient files were analyzed using IBM SPSS Statistics, version 25 (IBM Corp., Armonk, NY, USA). The categorical data are presented as numbers and percentages, and continuous variables are presented as mean and standard deviation. Independent samples t-test was used to compare continuous variables between patients with and without PCS. Chi-square test was used to compare categorical variables between the groups with and without PCS. Statistical significance was defined as $p<0.05$.

RESULTS

Among the 1,343 infertile women, 67 (5%) were diagnosed with PCS. The ultrasonographic evaluation of women diagnosed with PCS revealed several characteristic features (Table 1). The most common finding was the presence of >4 pelvic veins with a diameter exceeding 4 mm, observed in 43.3% of PCS cases. Dilation of the left ovarian vein (>5 mm) was present in 34.3% of cases, followed by dilation of the right ovarian vein (>5 mm) in 32.8%. Tortuous veins were noted in 31.3% of the PCS group. Retrograde flow, a key indicator of

venous insufficiency, was identified in the left ovarian vein in 14.9% of cases and in the right ovarian vein in 4.5% of cases.

Analysis of demographic and infertility-related variables (Table 2) revealed several significant distinctions between infertile women with and without PCS. Among the infertile cohort, significantly lower numbers of women were defined as secondary infertile (4.5% vs. 21.2% in controls, $p=0.001$) with a matching significant low gravida number compared to control group (0.07 vs 0.34 in controls, $p=0.007$). A particularly notable finding was the significantly lower mean total antral follicle count (AFC) in the PCS group (9.3) compared to the control group (12.9) ($p<0.001$). No statistically significant differences were observed in age, body mass index, duration of infertility, or follicle stimulating hormone levels between the two groups.

In terms of co-existing gynecological pathologies (Table 3), a significant difference was observed for the prevalence of PCOS, as none of the women with PCS (0%) had been diagnosed with it, whereas 17.3% of the control group had ($p<0.001$). No significant differences were found between PCS and endometriosis, hydrosalpinxes, or leiomyoma concurrence.

Table 1. Ultrasonographic findings of women with pelvic congestion syndrome

Ultrasound findings	Pelvic congestion syndrome (n=67) n, %
Left ovarian vein diameter >5 mm	23 (34.3)
Left ovarian vein retrograde flow	10 (14.9)
Right ovarian vein diameter >5 mm	22 (32.8)
Right ovarian vein retrograde flow	3 (4.5)
Tortious veins	21 (31.3)
>4 pelvic veins more than 4 mm in diameter	29 (43.3)

Table 2. Demographic variables of infertile women with and without pelvic congestion syndrome

	Pelvic congestion syndrome (n=67) n (%)	Controls (n=1276) n (%)	*p*
Secondary infertility	3 (4.5)	270 (21.2)	0.001*
Age (years)	32±5.1	32±5.2	0.9
Body mass index (kg/m²)	24.9±1.7	24.7±3.5	0.8
Infertility time (months)	113±60.3	102±59.3	0.1
Gravida	0.07±0.36	0.34±0.8	0.007
Follicle stimulating hormone	6.9±2.5	7.3±2.8	0.2
Total antral follicle count	9.3±4.4	12.9±5.8	<0.001**

*Chi-square test
**Independent samples t-test

Table 3. Gynecological pathologies in women with and without pelvic congestion syndrome

	Pelvic congestion syndrome (n=67) n (%)	Controls (n=1276) n (%)	*p*
Endometriosis	4 (6)	133 (10.4)	0.24
Hydrosalpinxes	4 (6)	70 (5.4)	0.8
Leiomyoma	10 (14.9)	211 (16.7)	0.7
Polycystic ovary syndrome	0	221 (17.3)	<0.001*

*Fisher's exact test

Table 4. Clinical symptoms in cases with respect to pelvic congestion syndrome

	Pelvic congestion syndrome (n=67) n (%)	Controls (n=1276) n (%)	*p*
Chronic pelvic pain	11(16.4)	39 (3.1)	<0.001*
Hemorrhoids	12 (17.9)	10 (0.8)	<0.001*
Dyspareunia	10 (14.9)	39 (3.1)	<0.001*
Dysmenorrhea	14 (20.9)	72 (5.6)	<0.001*
Menorrhagia	2 (3)	25 (2)	0.56
Left Lower extremity varices	6 (9)	39 (3.1)	0.009*
Right lower extremity varices	8 (11.9)	39 (3.1)	<0.001*
Vulvar varices	2 (3)	-	0.002**
Hematuria	2 (3)	2 (0.2)	0.01**

*Chi square, **Fisher's exact test

Finally, the analysis of clinical symptoms (Table 4) demonstrated significant differences between PCS and control group regarding a range of classical symptoms. CPP was reported by 16.4% of women with PCS, compared to only 3.1% in the control group ($p<0.001$). Dyspareunia (14.9% vs. 3.1%, $p<0.001$) and dysmenorrhea (20.9% vs. 5.6%, $p<0.001$) were also significantly more prevalent in the PCS group. Excluding symptoms of pain, hemorrhoids (17.9% vs. 0.8%, $p<0.001$), left lower extremity varices (9% vs. 3.1%, $p=0.009$), right lower extremity varices (11.9% vs. 3.1%, $p<0.001$), vulvar varices (3% vs. 0%, $p=0.002$) and hematuria (3% vs. 0.2%, $p=0.01$) symptoms were significantly more common in the PCS group. Menorrhagia was not found to be significantly more common in women with PCS compared to those without PCS in this cohort.

DISCUSSION

This large cross-sectional study of 1,343 infertile women found a 5% prevalence of PCS using strict sonographic criteria. This finding is clinically significant, suggesting PCS may be a previously underrecognized factor in as much as 1 in 20 of female infertility cases. Previous studies have shown that the overall prevalence of PCS in the general female population ranges from 6% to 27%. Among cohorts with CPP, PCS accounts for 15% to 30% of cases. The 5% prevalence observed in this study, which involved an infertile population, is at the lower end of this spectrum, and significantly lower than that of cohorts specifically selected for CPP. The reason for this difference may be that the studies conducted to determine the prevalence of PCS in the literature are calculated by retrospectively examining pelvic computerized tomographs and magnetic resonance images taken for different reasons, unlike the methodology used in this study. Infertile patients are expected to have fewer pregnancies on average compared to the general population, which supports the augmenting effect of having a pregnancy in the etiology of PCS.[12] In addition, the average age of the infertile patient group is lower than the average age at which PCS is first diagnosed in the general population, which is at 36 years old. This may also explain the lower prevalence.[13]

An unexpected finding was that women with PCS in this study had a significantly lower number of prior births (Table 2). This observation stands in contrast to the established understanding that PCS primarily affects multiparous women and often develops or worsens with subsequent pregnancies due to increased intravascular volume and venous distension.[6,12,14] This apparent contradiction suggests a potential selection bias in an infertility clinic setting. Women presenting for infertility treatment may have primary infertility or secondary infertility due to reasons other than PCS. The data implies that PCS, when identified in an infertile population, might be linked to mechanisms of primary infertility rather than being solely a consequence of multiple pregnancies. This finding challenges the traditional view of PCS as exclusively a "multiparous woman's disease" and encourages future research for investigating its role in primary infertility, potentially through direct impact on ovarian function or anatomical integrity from an early stage, independent of the physiological stresses of prior pregnancies.[9]

Another significant finding was the lower mean total AFC in the PCS group (Table 2). AFC is a widely accepted marker of ovarian reserve, and a lower count indicates diminished ovarian reserve, a crucial factor in female infertility.[15] The significantly lower AFC in women with PCS suggests a direct, fundamental impact of the condition on ovarian health and function, rather than solely mechanical or flow-related issues with fallopian tubes or the uterus.[16] The venous congestion, altered hemodynamics, and increased pressure in the pelvic veins associated with PCS could potentially compromise the microcirculation to the ovaries.[17] This could lead to chronic hypoxia, impaired nutrient delivery, or the accumulation of metabolic waste products within the ovarian microenvironment.[18] Such adverse conditions might accelerate follicular atresia or impair follicular development, thereby reducing the functional ovarian reserve.[19] This finding proposes a novel mechanism by which PCS could contribute to infertility, particularly primary infertility, warranting further mechanistic studies into the ovarian microenvironment in the presence of venous congestion.

None of the patients with PCS in the study cohort had PCOS, although the rate in the infertile women was around 17%. PCOS is a common endocrine disorder and a leading cause of anovulatory infertility.[20] PCS, in contrast, is primarily a vascular disorder. The observation that these two common causes of infertility appear to be mutually exclusive in this cohort suggests that the underlying pathophysiological mechanisms or predisposing factors for PCS and PCOS may be distinct. However, some other published studies report that the ovaries of PCS patients have a predominantly polycystic appearance due to venous congestion.[21-23] Although these studies do not place the appearance in a definitive category as polycystic ovary syndrome, it is clear that studies targeting this should be designed to clarify whether a morphologically similar antral follicle distribution pattern is causally related to pelvic congestion. In addition, PCOS, by its mechanism, creates a hyperandrogenenic microenvironment, whereas the mechanism of PCS is through the effect of the estrogenic microenvironment on the vessels.[24] Therefore, whether having PCOS is preventive for PCS is a separate research topic although the findings of this study support this hypothesis.

The absence of significant differences between PCS and our control group regarding the other gynecological pathologies, such as endometriosis, hydrosalpinxes, or leiomyoma, further indicates that PCS operates independently of these common gynecological conditions in this particular cohort.

The study strongly reinforces the well-documented clinical presentation of PCS by demonstrating significant differences between PCS and the control group in terms of a range of classic symptoms. These include CPP, dyspareunia, and dysmenorrhea, which are consistent with the established literature on PCS.[1,5,6]

Higher prevalence of hemorrhoids and lower extremity varices reinforces the understanding that PCS is often part of a broader

systemic venous insufficiency.[8] Increased pelvic venous pressure can affect other venous drainage systems, leading to varicose veins in the legs, vulva, and perianal region.[25,26] The significant presence of vulvar varices and both left and right lower extremity varices further supports this systemic venous component.[27,28]

An interesting and potentially novel symptom concurrence identified was with hematuria, present in 3% of PCS cases compared to 0.2% in controls. This finding suggests potential involvement of peri-vesical venous plexuses in PCS, where venous congestion around the bladder could lead to microscopic or macroscopic blood in the urine.[29,30]

The observed strong concurrences between PCS and these specific symptoms mean that these indicators, even if not the primary reason for seeking fertility treatment, should serve as important "red flags" for fertility specialists. In an infertility clinic, patients might not primarily complain of pain, or their pain might be dismissed as secondary to other infertility causes. Therefore, a comprehensive symptom history, specifically inquiring about these associated symptoms, should be mandatory during the initial workup of infertile women. This approach could lead to earlier suspicion and targeted diagnostic evaluation for PCS, uncovering an otherwise overlooked cause of infertility and guiding appropriate management.

The study's findings provide empirical support for the hypothetical links between PCS and impaired fertility. The significantly lower AFC in the PCS group strongly supports the hypothesis of direct ovulatory dysfunction or diminished ovarian reserve due to chronic venous congestion. Furthermore, the lower gravida and secondary infertility rates observed in this study suggest that PCS might be contributing to primary infertility, potentially through these direct ovarian effects, rather than being a consequence of multiple pregnancies. While this study is cross-sectional and cannot establish causality, its data reinforces the probability of PCS affecting fertility through mechanisms impacting ovarian function, fallopian tube integrity, and uterine receptivity.

This study reiterates the importance of increased awareness among fertility specialists regarding PCS as a potential contributing factor to female infertility. The findings suggest systematic screening, particularly with ultrasonography, for PCS in infertile women. This is especially relevant for those presenting with unexplained infertility, lower AFC, or any of the significantly associated symptoms identified in this study, such as CPP, dyspareunia, dysmenorrhea, hemorrhoids or external varices.

Addressing PCS through medical management or minimally invasive procedures, like pelvic vein embolization may not only alleviate pain but also potentially improve fertility outcomes. While existing studies on fertility improvement post-embolization are limited, they offer encouraging results.

The current study possesses several notable strengths. Its substantial sample size of 1,343 infertile women provides important statistical power for identifying associations and lends credibility to the observed prevalence and characteristic profiles. The prospective nature of the study and the use of a single, highly experienced in vitro fertilization specialist for all ultrasonographic examinations significantly reduced inter-observer variability, thereby enhancing the consistency and reliability of the diagnostic data. Furthermore, the thorough collection of demographic variables, urogynecological and pelvic pain symptomatology, and detailed ultrasound findings allowed for a comprehensive characterization of the study participants.

Despite its strengths, the study has inherent limitations. As a cross-sectional observational study, it can establish associations and prevalence but cannot definitively determine causality. The study cannot conclude that PCS causes infertility or the observed demographic or symptomatic differences; it only shows co-occurrence at a single point in time. The single-center design, conducted at one infertility clinic, may limit the generalizability of the findings to other populations or healthcare settings, as patient demographics, referral patterns, and diagnostic practices can vary between centers. In addition, as the study cohort was pre-selected for infertility, the findings may not be representative of PCS prevalence or characteristics in the general female population or in women with PCS who do not present with infertility.

Ultrasonography, particularly in a supine position, may not always fully capture the complete extent of pelvic varicosities, which can be more evident with upright positioning or more advanced imaging techniques, such as venography, computed tomography or magnetic resonance imaging. However, the study's inclusion of the val-salva maneuver and positional changes during examination eliminates some of these limitations. Finally, our study design does not include follow-up data on fertility outcomes after PCS diagnosis or potential treatment, which prevents conclusions about the impact of PCS management on reproductive success.

Based on the findings of this study, several suggestions can be made for future research. Prospective longitudinal studies will be important to investigate a causal relationship between PCS and infertility, tracking fertility outcomes over time in women diagnosed with PCS. Randomized controlled trials are needed to evaluate the efficacy of PCS treatments, such as embolization, specifically on fertility outcomes. Further research should be conducted to understand the ways PCS might affect ovarian reserve, potentially through studies on ovarian microcirculation or hormonal regulation in PCS patients, and to explore the reasons behind the observed negative association with PCOS. Larger multicenter studies are also encouraged to validate the prevalence and associated features of PCS in diverse infertile populations, improving generalizability. Finally, the development and validation of standardized diagnostic protocols for PCS within infertile groups would be highly beneficial.

CONCLUSION

This study identified a 5% prevalence of PCS in infertile women and its key features, which included dilated pelvic and ovarian veins, fewer prior pregnancies, and diminished ovarian reserve shown by lower AFC. The findings revealed a negative co-existence with PCOS and significant differences between groups in terms of symptoms including CPP, dyspareunia,

dysmenorrhea, and varices. These results suggest PCS may have a role in primary infertility and altered ovarian function. The study highlights the importance for reproductive medicine practitioners to consider PCS during infertility workups and the value of diagnostic efforts towards PCS to reveal treatable infertility causes and improve reproductive outcomes.

Ethics

Ethics Committee Approval: Ethics approval had been obtained from Tekirdag Namik Kemal University Ethics Committee (approval number: 2024.52.03.16, date: 26.03.2024).

Informed Consent: Informed consent was obtained from all participants.

Authorship Contributions

Surgical and Medical Practices: E.A., Concept: B.Ü., B.D.T., A.İ.T., Design: B.Ü., B.D.T., F.D., Data Collection or Processing: E.A., F.D., A.İ.T., Analysis or Interpretation: B.Ü., B.D.T., A.İ.T., Literature Search: B.Ü., E.A., F.D., Writing: B.Ü.

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Original Article

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Polycystic Ovary Syndrome and Social Media Content: An Evaluation Through YouTube Videos and Instagram Reels Content

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ABSTRACT

Purpose: Polycystic ovary syndrome (PCOS) is a serious health condition, affecting 5-10% of women of reproductive age, and is associated with obesity, irregular periods, infertility, and hirsutism. PCOS may significantly impact quality of life and requires accurate information for proper management. Social media has become an important source where many women seek health information. This study evaluated YouTube and Instagram reels content related to PCOS. The search terms "PCOS," "PCOS and menstrual irregularity," and "PCOS and hair growth" were used. Identified content was assessed for quality, educational value, and number of views. The aim was to determine whether these platforms provide reliable, high-quality educational information about PCOS.

Methods: Content was categorized into four groups according who created it: physicians; healthcare institutions; non-physician healthcare professionals; and personal accounts. For each YouTube and Instagram video, the following variables were recorded: duration, resolution, likes, comments, upload date, Global Quality score (GQS), modified DISCERN (mDISCERN), and engagement rate. This categorization allowed comparisons between professional and non-professional content producers.

Results: Content created by physicians and healthcare institutions demonstrated significantly higher GQS and mDISCERN scores than that produced by other groups. Physicians reached smaller audiences but generated higher engagement, while personal accounts attracted more views and interactions overall. These findings highlight the dual nature of social media as both a valuable source of information and a potential channel for misinformation.

Conclusion: Content from physicians and healthcare institutions was more accurate and reliable, whereas personal accounts gained greater popularity. This study demonstrated that popularity does not necessarily reflect quality. Medical information on social media should prioritize accuracy and reliability in order to genuinely benefit users and reduce the risk of misinformation.

Keywords: Polycystic ovary syndrome, YouTube, Instagram, interaction rate

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a serious health condition, affecting 5-10% of women of reproductive age, and is associated with obesity, impaired glucose tolerance, irregular menstrual cycles, infertility, and hirsutism.[1] YouTube is a popular platform where users can easily access video content and share these videos.[2] Visitors can upload videos, like or dislike content, and express their opinions through comments. Although YouTube can be used as a source of medical information, videos on the platform are not peer-reviewed. Moreover, videos that do not meet educational content criteria are ranked according to factors such as popularity, view counts, and comments.[3] Instagram is a platform where users can post photos and short videos, which can be liked, commented on, and shared. While Instagram can serve as a source of medical information, posts on the platform are also not peer-reviewed.[4] In this study, YouTube videos and Instagram reels were searched for using the keywords "polycystic ovary syndrome," "PCOS," "PCOS and irregular menstruation," and "PCOS and hirsutism". Identified content was evaluated in the order presented to users by the platform algorithms. A total of 50 YouTube videos and 50 Instagram reels were analyzed. Content was categorized into four groups according to the creating source: physicians; healthcare institutions; non-physician healthcare professionals; and personal accounts.

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This study evaluated the educational quality, reliability, and popularity of PCOS-related YouTube videos and Instagram reels. The aim was to examine the content quality of PCOS-related videos on YouTube and Instagram and assess the extent to which viewers could access accurate information from these videos. To the best of our knowledge, this is the first study to analyze and evaluate both Instagram and YouTube content on PCOS in the manner described.

METHODS

All data used in this study were publicly available and did not require special access for collection. Therefore, no permission was required from an ethics committee, YouTube or Instagram to conduct this study. In March 2025, the most viewed English-language content was identified using the keywords "polycystic ovary syndrome," "PCOS," "PCOS and irregular menstruation," and "PCOS and hirsutism." The selected content was independently evaluated by two obstetricians and gynecologists in a double-blind design, and a third obstetrician's opinion was sought in cases of disagreement. Interobserver agreement was assessed using Cohen's kappa statistic. Videos that were non-English, produced for advertising purposes, or explicitly intended to manipulate viewers were excluded. Data collection was performed during a single time period (March 2025).

Given the lack of sufficient published data regarding potential seasonal fluctuations in PCOS-related social media content, a fixed time window was used to enhance reproducibility. This approach was adopted to minimize the effects of algorithmic changes and potential seasonal variations. For the purposes of the study, new accounts were created specifically for research on the respective platforms. YouTube and Instagram content was accessed via web browsers on a computer, and all evaluations were conducted using the browsers' incognito mode. This method was chosen to minimize the risk of selection bias caused by platform algorithms that provide personalized content recommendations.

Content was evaluated starting from the first page of search results on YouTube and Instagram search engines. For each YouTube video, the following variables were recorded: video length, video resolution, number of views, number of likes, number of comments, upload date, Global Quality score (GQS), modified DISCERN (mDISCERN) score, and engagement rate. For a description of the GQS and mDISCERN scoring system and validation, see below. Account size (followers/subscribers) and account age were deliberately excluded from analysis to better reflect the real user experience. In this study, content encountered according to the ranking provided by the platforms' algorithms was assessed, and analysis was performed based on absolute engagement values and quality metrics. All quantitative data were manually recorded by the researchers for each video or reel, using pre-defined standardized forms to ensure consistency.

Videos with durations between 1 and 10 minutes were included. The number of dislikes for YouTube videos could not be recorded because YouTube hides dislike counts. The study initially planned to calculate a video power index (VPI) to assess video impact, using the formula: [likes/ (likes + dislikes)] × 100.[4] However, VPI could not be calculated as dislike counts are not officially shared by YouTube with third parties. For each video, values such as likes/day, comments/day, and views/day were calculated based on the elapsed time since publication, total views, likes, and comments. In addition, the like-to-view ratio was calculated as an indicator of viewer satisfaction, reflecting the proportion of viewers who liked the content, independent of total views.

From Instagram posts, reels were included in the study. Instagram reels are short, easily consumable videos with a maximum length of three minutes. For each reel, fluency, audio and video quality, number of likes, number of comments, number of times the reel was shared via direct message (DM), and the posting date were recorded. Reels were evaluated using the GQS and interaction rate. For each Instagram reel, likes/day, comments/day, and DMs/day were calculated. The DMs/day metric represents the frequency of organic sharing of the content via DM calculated by dividing the total number of DMs by the number of days since posting. Both YouTube videos and Instagram reels were also scored using the mDISCERN tool.

Modified DISCERN Scoring

The DISCERN tool is a standardized scoring system used to evaluate the quality of medical content.[5] The mDISCERN is a simplified, five-question version of the original DISCERN instrument, which has been used in multiple previous studies.[6-8] For mDISCERN scoring, five "yes" or "no" questions were asked. A "yes" response was scored as 1 and a "no" as 0, resulting in a total score out of 5. The five questions were:

1. Is the aim clear, concise, and understandable?
2. Are the sources of information reliable? (Are cited references or video content derived from valid studies?)
3. Is the information presented balanced and unbiased? (Is there any reference to alternative treatment options?)
4. Are additional sources of information listed?
5. Does the video address areas of uncertainty?

Interpretation of the DISCERN Scores

- 1-2 points: Low quality. Material is insufficient in terms of reliability and information presentation and is not suitable for educational or patient information purposes.
- 3-4 points: Moderate quality. Material contains some important information but has deficiencies and imbalances; it may be partially useful.
- 5 points: High quality. Material presents reliable and balanced information and is highly suitable for education and patient information.

Global Quality Score

Videos were also evaluated using the GQS, a five-point scale assessing the overall quality of video content.[9] GQS evaluates the educational value of the content based on five core criteria.[8]

GQS Scoring Table (Text Version)

Score 1: Very poor quality - very low quality, poor flow, most information missing, not useful for education. Score 2: Poor quality - limited usefulness; only some information is available, most key points not addressed. Score 3: Moderate quality and flow - somewhat useful but important topics are missing; flow is insufficient. Score 4: Good quality and flow - useful, as most key topics are addressed. Score 5: Excellent quality and flow - highly useful, covering all important topics comprehensively.

Interaction Index

The interaction index is a holistic measure of content engagement over time, allowing performance to be evaluated not only by total interactions but also in relation to time.

Formula (Text Version)

Interaction index = (number of likes + number of comments + number of shares) ÷ number of days.

Engagement Rate

Engagement rate is a key performance metric indicating the extent of interaction between content and viewers. This ratio typically includes likes, comments, and sometimes negative feedback (dislikes) relative to total views. However, since YouTube no longer publicly displays dislike counts, standard calculation methods have been adjusted.

In this study, the engagement rate was calculated using only likes and comments relative to total views. This provides a usable and comparable measure of overall viewer interaction.

Formula (Text Version)

Engagement rate = [(number of likes + number of comments) ÷ total views] × 100

Videos were categorized into four main groups according to their source:

1. Videos produced on behalf of healthcare institutions
2. Videos produced by physicians
3. Videos produced by non-physician healthcare professionals
4. Personal videos produced by individuals who are not healthcare professionals

YouTube videos were excluded from the study if they were longer than 10 minutes or shorter than 1 minute, if the language of the content was not English or English was insufficiently understandable, if video quality was below 480p, if the video contained advertisements, or if there was a mismatch between the title and the content. Videos included in the study were English-language content longer than 1 minute and shorter than 10 minutes, with video quality above 480p, matching title and content, and without advertising. Videos below 480p reduce educational value, as medical visuals, diagrams, or written materials may not be clearly visible. This criterion ensures that visual content can be properly evaluated. Videos shorter than 1 minute cannot adequately address complex topics such as PCOS, while videos longer than 10 minutes do not reflect typical social media consumption habits, considering user attention spans.

Instagram reels included in the study were excluded if the language was not English or English was insufficiently understandable, or if they contained advertising. Only English-language reels without advertising were included. No time restriction was applied for Instagram reels.

A total of 114 YouTube videos were initially reviewed by the researchers (Figure 1). Based on inclusion and exclusion criteria, 61 videos were excluded for being longer than 10 minutes, 1 video for being shorter than 1 minute, and 2 videos for containing advertisements. Consequently, 50 videos were included for evaluation.

For comparisons between groups, the Shapiro-Wilk test indicated that the data were not normally distributed. Therefore, the non-parametric Kruskal-Wallis test was used.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 25.0 (IBM Inc, Armonk, NY, USA). In group comparisons using the Kruskal-Wallis test, $p<0.05$ was considered statistically significant, $p<0.001$ was considered highly significant, and $p>0.05$ was considered not significant.

A total of 55 reels were viewed for Instagram reels content. As a result of inclusion and exclusion criteria, two pieces of content were excluded due to advertising, two pieces of content were excluded due to awkward language, and one piece of content was excluded due to title-content mismatch. As a result, 50 individual Instagram reels were evaluated (Figure 2).

RESULTS

Interobserver reliability analysis demonstrated high agreement. For GQS scores, $\kappa=0.847$ ($p<0.001$), and for mDISCERN scores, $\kappa=0.724$ ($p<0.001$). These values correspond to “almost perfect” and “good” levels of agreement, respectively.

Of the YouTube videos included in the study, 18 were posted on personal accounts, three by non-physician healthcare workers, 16 by doctors, and 13 by healthcare institutions. The GQS, mDISCERN, engagement rate, views/day, likes/day, likes/views, and average duration values are shown in Table 1. Content created by doctors demonstrated the best performance in terms of quality and engagement, although their like rate was low. The overall quality of doctors’ content was notably high. Since the mDISCERN score is a measure of the reliability and accuracy of content, it indicates that the videos produced by doctors provide reliable and accurate information. Personal accounts were found to be highly popular in terms of views and likes; however, their reliability scores were low. Compared to other categories, personal accounts ranked lower in terms of content quality and accuracy. This suggests that personal accounts provide less reliable information or are more oriented toward entertainment content. Healthcare organizations maintained high content reliability, but their engagement and viewership rates were low. A substantial difference was observed between non-physician healthcare professionals and personal accounts; while personal accounts received far more views and engagement, the content of healthcare professionals received fewer views and interactions. The very

low interaction rate of non-physician healthcare professionals compared to other groups may indicate that their content has difficulty establishing a strong connection with the audience or that the level of audience interest is low.

Of the Instagram reels content included in the study, 21 were posted by doctors, eight by non-physician healthcare professionals, 17 by personal accounts, and four by healthcare organisations.

On both platforms, some personal accounts were found to introduce themselves to people with unrealistic, false statements such as "PCOS coach" and mislead them in this way. This statement is not a variable systematically analyzed within the scope of our study, but rather a qualitative finding observed during the content evaluation process. The average GQS score for Instagram reels, the average mDISCERN score, the average number of likes per day, the average number of posts per day, and the average number of comments per day for doctors, non-physician healthcare workers, personal accounts, healthcare institutions are shown in Table 2. Instagram reels produced by physicians had high GQS and mDISCERN scores and were evaluated as high-quality and reliable. These scores indicate that the content was strong, both esthetically and in terms of informational accuracy. Content produced by non-physician healthcare professionals demonstrated lower reliability compared to physicians, although it generally provided an adequate level of information.

Content from personal accounts received lower GQS and mDISCERN scores relative to other categories, reflecting that

Table 1. YouTube content analysis table

Category	GQS score	mDISCERN score	Engagement rate	Views/day	Likes/day	Likes/ views	Average duration (sec)
Doctors	2.87	4.0	5.76	55.6	1.42	0.05	319.6
Non-physician healthcare workers	2.5	3.0	0.94	24.7	0.3	0.008	318.6
Personal accounts	2.5	2.26	4.68	644.5	16.4	0.04	253.3
Healthcare institutions	3.3	3.7	1.1	191.8	2.97	0.01	176.2
Overall average	2.84	3.29	3.84	305.72	7.25	0.03	256.7

GQS: Global Quality score, mDISCERN: Modified DISCERN

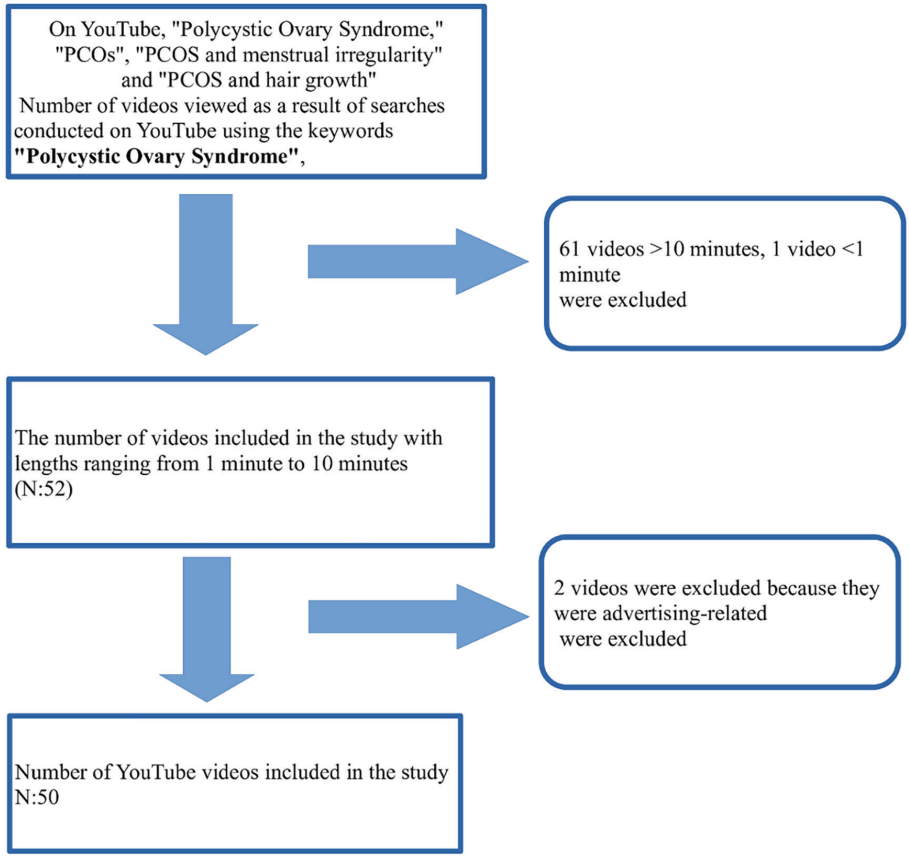

Figure 1. YouTube video inclusion and exclusion scheme for the study
PCOS: Polycystic ovary syndrome

personal accounts typically offer more entertainment-oriented or subjective content. The engagement rate for personal accounts was moderate; although not high, the content was still viewed and interacted with by audiences.

Content from healthcare institutions exhibited both reliability and quality, indicating that these accounts provide professional and scientifically accurate material. Physicians and healthcare institutions achieved the highest reliability scores. However, while healthcare institutions received lower engagement, physicians achieved higher engagement and more direct interaction with viewers through messages.

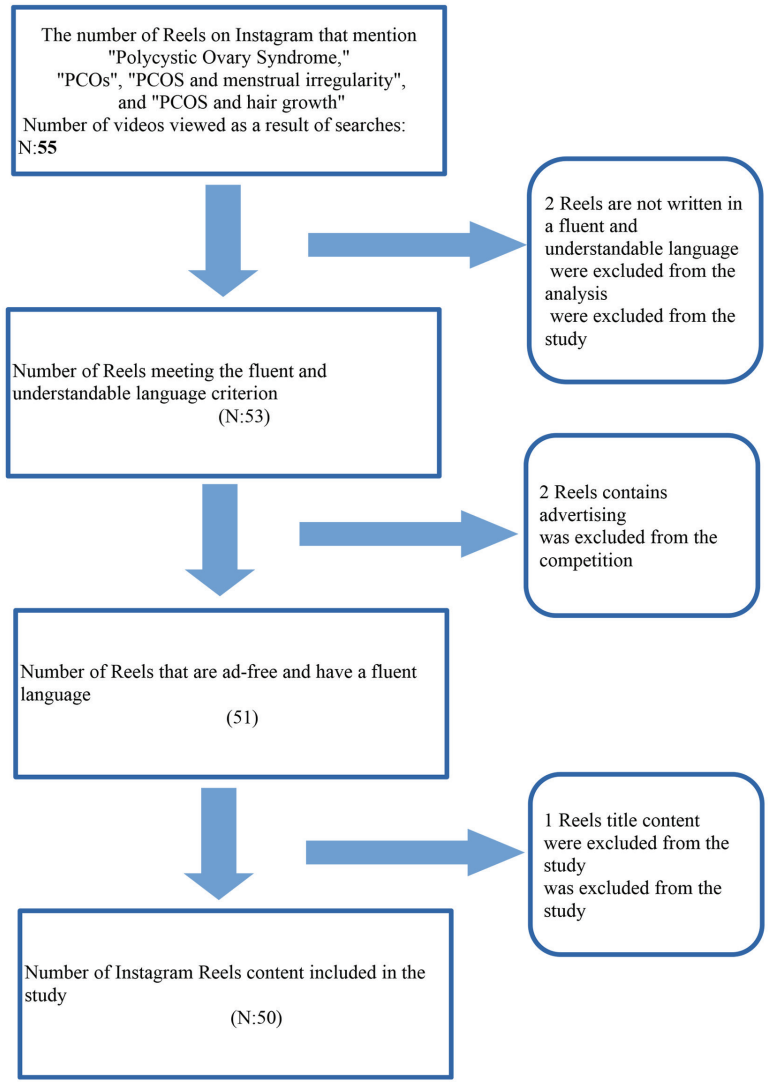

Figure 2. Scheme for including or excluding Instagram reels content from the study

PCO: Polycystic ovary syndrome

Table 2. Instagram reels data averages

Category	GQS score	mDISCERN score	Interaction index	Likes/day	DM/day	Comments/day
Doctors	3.35	4.19	923.0	0.058	283.21	14.9
Non-medical health workers	2.87	3.00	5977.4	0.126	579.5	31.7
Personal accounts	2.26	2.20	438.27	0.27	217.5	43.6
Healthcare institutions	3.37	4.62	28.4	5.5	10.2	0.12
Overall average	2.91	3.32	712.7	0.52	295.5	26.08

GQS: Global Quality score, mDISCERN: Modified DISCERN, DM: Direct message

Non-physician healthcare professionals exhibited notable engagement, particularly in DM and comment counts, although their content reliability was lower than that of physicians. Personal accounts stood out with high numbers of likes and comment counts but lower reliability scores. Overall, personal accounts appear to generate more engaging content, yet the content quality is generally more subjective.

The results of the Kruskal-Wallis test are presented in Table 3 and Table 4, which contain analyses of YouTube and Instagram content, respectively.

YouTube is a platform where content tends to be longer and more detailed, allowing reliable sources such as physicians and healthcare institutions to demonstrate stronger credibility. In contrast, Instagram emphasizes shorter content, where the reliability of content producers, particularly personal accounts and non-physician healthcare professionals, is generally lower.

Due to Instagram's focus on rapid and visually-oriented content, engagement rates may be higher. Personal accounts and non-physician healthcare professionals received notable engagement on this platform, whereas more institutional content, such as that produced by healthcare institutions, tends to have lower engagement rates.

On YouTube, engagement rates are generally lower compared to Instagram, as viewers prefer longer-duration content. However, the depth of content on YouTube tends to sustain engagement over a longer period.

DISCUSSION

The internet is widely used as a source of health information.[10] YouTube and Instagram are commonly used social media platforms that individuals also consult for informational purposes. However, on these platforms, content may spread rapidly regardless of its accuracy, posing a risk for the dissemination of misinformation. Considering the increasing frequency of online searches regarding PCOS over time, the reliability of content on these platforms has become particularly important.[11] The aim of this study was to examine this issue.

In a study by (Mahajan et al.[12]) titled Educational quality and content of YouTube videos on diabetic macular edema (International Ophthalmology), findings aligned with our results, showing that content produced by physicians and healthcare institutions was of higher quality compared to content from other producers. Similarly, in the present study, content produced by physicians and healthcare institutions had significantly higher GQS and mDISCERN scores than that produced by other groups. Regarding YouTube content, videos produced by healthcare institutions had an average GQS of 3.3, exceeding the overall mean of 2.84, while physicians ranked second with an average of 2.87. For mDISCERN scores, physicians, assessed by physicians, ranked first with an average of 4.0, and healthcare institutions ranked second with an average of 3.7. These findings were supported by significant differences, indicating that physicians and healthcare institutions produce more reliable and higher-quality content. Post hoc analyses confirmed these differences, showing that physicians significantly outperformed personal accounts in content quality metrics on both YouTube and Instagram platforms ($p<0.05$ for all comparisons), while personal accounts achieved higher engagement rates (Tables 5 and 6).

In terms of views per day and likes per day, personal accounts had the highest average counts. Although these differences approached statistical significance ($p=0.06$-0.07), they were not definitive; nevertheless, personal accounts appear to be more successful in reaching content consumers. In terms of like-to-view ratios, physicians had higher average values, though this difference was again not significant ($p=0.44$). This suggests that, although the audience reached by physicians was smaller, engagement within this audience may be higher.

In terms of video duration, healthcare institutions produced shorter videos, whereas physicians produced longer videos. A similar trend was observed in the analysis of Instagram reels. Healthcare institutions had the highest scores in GQS (3.37) and mDISCERN (4.62), and these differences were significant. Physicians ranked second with average scores for GQS and DISCERN of 3,35 and 4.19, respectively. This suggests that physicians and healthcare institutions also produced higher-quality content on Instagram.

Although healthcare institutions had the highest average likes per day, this difference was not significant ($p=0.26$); therefore, this difference should be interpreted cautiously. When evaluating DM/day and comments/day, personal accounts and non-physician healthcare workers had higher average engagement, with the difference for comments/day being significant ($p=0.04$). This suggests that content produced by these two groups may have greater potential for sharing and discussion. Although physicians' DM/day values were above the average, their likes/day and comments/day were lower. A possible reason for this was that their content was informative but did not sufficiently attract users in terms of visual or emotional engagement.

Table 3. Statistical comparison of YouTube data

Metric	H-statistic	*p*-value	Effect size
GQS	9.8	0.0196	0.248
mDISCERN	33.16	0.0000003	0.455
Views/day	7.43	0.0592	0.127
Likes/day	6.92	0.0745	0.153
Likes/views	2.67	0.445	0.064

GQS: Global Quality score, mDISCERN: Modified DISCERN

Table 4. Statistical comparison of Instagram reels data

Metric	H-statistic	*p*-value	Effect size
GQS	9.8	0.0196	0.259
mDISCERN	33.16	0.0000003	0.641
Likes/day	3.94	0.2675	0.038
DM/day	3.17	0.3658	0.046
Comments/day	8.28	0.0405	0.109

GQS: Global Quality score, mDISCERN: Modified DISCERN, DM: Direct message

Table 5. Instagram reels post hoc analysis results

Variable	Group 1	Group 2	Mean difference	*p*-value	Lower confidence interval	Upper confidence interval
GQS	Doctor	Personal account	-1.16	0.0028	-1.98	-0.33
GQS	Doctor	Non-physician healthcare staff	-0.55	0.47	-1.56	0.46
GQS	Doctor	Healthcare institution	-0.05	1	-1.37	1.27
GQS	Non-physician healthcare staff	Personal account	-0.61	0.42	-1.67	0.45
GQS	Non-physician healthcare staff	Healthcare institution	0.50	0.8	-0.98	1.98
GQS	Personal account	Healthcare institution	1.11	0.15	-0.25	2.47
mDiscern	Doctor	Non-physician healthcare staff	-1.15	0.0028	-1.97	-0.33
mDiscern	Doctor	Personal account	-1.98	0.0001	-2.65	-1.31

GQS: Global Quality score, mDISCERN: Modified DISCERN

Table 6. YouTube videos post hoc analysis results

Variable	Group 1	Group 2	Mean difference	*p*-value	Lower confidence interval	Upper confidence interval
GQS	Physician	Personal accounts	0.85	0.012	0.20	1.50
GQS	Physician	Healthcare institution	0.45	0.401	-0.38	1.28
GQS	Personal accounts	Healthcare institution	0.80	0.051	-0.00	1.59
mDiscern	Physician	Personal accounts	0.90	0.018	0.15	1.65
mDiscern	Physician	Healthcare institution	0.52	0.280	-0.29	1.33
mDiscern	Personal accounts	Healthcare institution	0.87	0.027	0.09	1.65
Engagement rate	Physician	Personal accounts	6.20	0.022	1.10	11.30
Engagement rate	Physician	Healthcare institution	-4.61	0.450	-13.80	4.58
Engagement rate	Personal accounts	Healthcare institution	-3.76	0.563	-12.60	5.09

GQS: Global Quality score, mDISCERN: Modified DISCERN

Similarly, in a study on contraceptive implants Sütcüoğlu and Güler[13], the quality and reliability of social media videos were evaluated using GQS and mDISCERN scores, showing that content created by healthcare professionals was of higher quality. In the present study, physicians and healthcare institutions also produced higher-quality content, whereas personal accounts achieved higher views and engagement. This finding demonstrated that on social media platforms, information quality should be assessed independently of popularity. In particular, health-related content should be evaluated using systematic quality-based criteria, rather than relying solely on engagement metrics.

The limitations of this study include the restricted number of content items, low variability between groups, and the tendency of social media platform algorithms to prioritize engagement metrics over content quality. These findings highlight that healthcare professionals analyzing social media should consider not only statistical data but also the algorithmic promotion mechanisms of the platforms. Another limitation was that the GQS and mDISCERN scoring systems were originally developed for traditional-format videos. However, their core evaluation criteria (source reliability, information balance, and clarity of purpose) are format-neutral and applicable to short-format content. From the patient perspective, the accuracy and reliability of health information are independent of content duration.

Study Limitations

Additional limitations include the restricted sample size, low intergroup variability, and the platforms' emphasis on engagement metrics over content quality when ranking content. Future research may address this methodological gap by developing scoring systems optimized for short-format social media content. Furthermore, the applied duration (1-10 minutes) and resolution (>480p) criteria may have excluded potentially valuable educational content. Specifically, longer, detailed educational videos or lower-resolution but content-rich materials were excluded from evaluation. Future studies may consider applying these criteria more flexibly.

CONCLUSION

Overall, content produced by physicians and healthcare institutions scored higher in information accuracy on both platforms, whereas personal accounts achieved higher views and engagement. This underscores the importance of evaluating the source of content, as certain material, presented using terms such as "PCOS coach", may create the impression of professional medical authority for viewers. For medical content on platforms such as YouTube and Instagram to be beneficial, both users and content creators should pay careful attention to the accuracy and reliability of the information presented.

Ethics

Ethics Committee Approval: Since the study is open to the public, ethics committee approval is not required.

Informed Consent: Not required.

Footnotes

Authorship Contributions

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Original Article

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Comparison of Oocyte Yield in Medical, Social or Donor Oocyte Cycles

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ABSTRACT

Purpose: To compare oocyte yield, maturation rates, cumulative vitrified oocyte counts, incidence rate of ovarian hyperstimulation syndrome (OHSS), and clinical-demographic factors influencing efficiency in oocyte cryopreservation cycles performed for donor and social fertility preservation purposes.

Methods: A retrospective cohort analysis was conducted on 1,041 women who underwent oocyte pick-up and vitrification between 2020 and 2024 in four private in vitro fertilization centers. Participants were grouped into donor (n=590) and social (n=451) cohorts. Clinical, hormonal, stimulation protocol data and oocyte outcomes were compared between groups.

Results: The mean age was 24.8 and 34.4 years in the donor and social group, respectively ($p<0.001$). Donors had lower basal follicle stimulating hormone and higher anti-Müllerian hormone concentrations and antral follicle counts. The mean total gonadotropin dose was 1,516 international unit (IU) in donors and 3,425 IU in the social group ($p<0.001$). Ovulation triggering was predominantly performed with human chorionic gonadotrophin; in 88.3% of donors versus 76% of the social group. Mean number of retrieved oocytes was 39.5 in donors and 5.0 in the social group; mature (30.4 vs. 4.3) and vitrified oocyte counts (23.0 vs. 4.7) were significantly higher in donors ($p<0.001$). OHSS incidence was 14.7% in donors and 1.3% in the social group. Most social group participants were self-funded, reflecting a higher socioeconomic status and fertility preservation, motivated by career planning.

Conclusion: Significant socio-demographic, biological, and clinical differences existed between donor and social groups undergoing oocyte cryopreservation in the study population. These findings highlight the importance of individualized stimulation protocols and counseling tailored to patient profiles. Data from this study may aid optimization of fertility preservation strategies and resource allocation.

Keywords: Oocyte cryopreservation, fertility preservation, oocyte donation, social freezing, ovarian stimulation, oocyte yield, vitrification, ovarian hyperstimulation syndrome, reproductive outcomes, assisted reproductive technology

INTRODUCTION

Oocyte cryopreservation is the process of freezing mature metaphase II (MII) oocytes obtained from women in a laboratory setting for long-term storage. This technique halts the biological aging process of oocytes, thereby enabling the possibility of becoming pregnant in later years. Today, a rapid freezing method known as vitrification ensures high success rates by preserving the structural integrity of the oocytes.[1]

Within modern assisted reproductive technologies, oocyte cryopreservation is gaining increasing importance and is based on three main indications. Medical indications aim to preserve fertility in conditions that threaten reproductive potential, such as malignancies (e.g., breast or hematologic cancers), autoimmune diseases, and gonadotoxic treatments.[2] Social indications address the desire of healthy women to preserve their fertility potential at an advanced age due to personal, professional, or social reasons for delaying pregnancy.[3]

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Donor cycles involve the freezing or preparation of oocytes obtained from young donors with high ovarian reserves for use by infertile couples, either for freezing or fresh transfer.[4]

This diversity in indications leads to significant differences in controlled ovarian hyperstimulation protocols, stimulation duration, gonadotropin dosages, and clinical objectives. Consequently, noticeable variations are observed in parameters such as the total number of oocytes retrieved, maturation rates, and the risk of complications.[2-4] Only a limited number of studies in the literature have directly compared social, medical, and donor cycles.

Existing findings indicate that obtaining a sufficient number of high-quality oocytes is critical for pregnancy success in social fertility preservation cycles at an advanced age, whereas in medical indications, due to time constraints, the yield is relatively limited. Donor cycles, on the other hand, are considered a reference group due to the high oocyte yield from young healthy donors.[5]

The aim of this study is to compare parameters, including total oocyte yield, proportions of mature and immature oocytes, maturation rates, cumulative number of vitrified oocytes, incidence of ovarian hyperstimulation syndrome (OHSS), and the frequency of oocyte pick-up (OPU) procedures in oocyte cryopreservation cycles performed for social, medical, and donor purposes. The findings may help the development of individualized approaches for fertility preservation practices and to provide a scientific basis for social fertility planning.

METHODS

Study Design

This study was a retrospective cohort analysis. The primary outcome of the study was oocyte yield per retrieval cycle, while secondary outcomes included oocyte maturation rates, cumulative vitrified oocyte counts, incidence of OHSS, and socio-demographic characteristics. The study included patients who applied to four private in vitro fertilization centers for oocyte cryopreservation between 2020 and 2024. A total of 1,041 women who underwent oocyte retrieval and vitrification procedures were identified, and their medical records were reviewed. The patients were evaluated under two categories: donor group and social group. Data were retrospectively obtained from patient files and digital archive records. All patient identities were strictly kept confidential.

Participants

Ethical approval for this study was granted by the Ethics Committee of Bolu Abant İzzet Baysal Faculty of Medicine (approval number: 2025/340, date: 21.07.2025). The study included patients who underwent at least one OPU procedure. The study population consisted of cases evaluated within the context of social (elective), medical (fertility preservation), or donor oocyte programs and who underwent vitrification following oocyte retrieval.

Inclusion criteria were: complete and accessible clinical records regarding the patient's stimulation protocols and oocyte yield, an age range between 18 and 42 years, and appropriate permissions obtained within the scope of ethics committee approval for data sharing.

Exclusion criteria included patients who did not undergo oocyte retrieval or vitrification, those with undefined indications, i.e., not clearly categorized as social, medical, or donor, patients with incomplete or untraceable data, women under 18 or over 42 years of age, cycles with severely diminished ovarian reserve and poor stimulation response (≤3 oocytes retrieved), cases canceled due to OHSS with no oocytes retrieved, transgender individuals, and patients undergoing gender transition.

Assessment

The cases included in the study were divided into two groups based on the indication for oocyte cryopreservation. The donor group (n=590) consisted of healthy women with a high ovarian reserve profile who donated their oocytes for use in infertility treatment. These individuals had no reproductive concerns of their own, participated solely as donors, and all costs related to the stimulation process were covered by the recipient couple or the clinic. The social group (n=451) comprised women who applied for elective (social) fertility preservation and sought to safeguard their reproductive potential due to advancing age. Individuals in this group aimed to preserve their own fertility for future family planning and personally bore all treatment-related expenses. Thus, the medical and social indication cases were combined into a single social group for the purposes of analysis.

All participants presented on the second or third day of menstruation, at which point transvaginal ultrasonography was performed to assess antral follicle count, and serum levels of follicle stimulating hormone (FSH), luteinizing hormone, estrogen, prolactin, and thyroid function tests were evaluated. In both groups, sociodemographic data, clinical and hormonal indicators [body mass index (BMI), FSH, anti-Müllerian hormone (AMH), baseline antral follicle count], controlled ovarian stimulation protocols (type of protocol used, total gonadotropin dose, triggering method), and oocyte yield and cycle outcomes (total and mature oocytes retrieved, proportion of cycles with >15 oocytes retrieved, number of vitrified oocytes, incidence of OHSS were analyzed comparatively. Mature oocytes were defined as MII oocytes confirmed under microscopy. OHSS was diagnosed according to the criteria of the American Society for Reproductive Medicine, based on clinical symptoms and laboratory findings.[6]

Statistical Analysis

Statistical analyses were performed using SPSS version 26.0 (IBM inc., Armonk, NY, USA).

The distribution of continuous variables was assessed using the Kolmogorov-Smirnov test.

Data with a normal distribution are expressed as mean ± standard deviation, while non-normally distributed data are expressed as median (min-max). For comparisons between groups, the independent samples t-test (for normally distributed data), the Mann-Whitney U test (for non-normally distributed data), and the chi-square test or Fisher's exact test (for categorical variables) were used. To identify factors

affecting oocyte yield, multivariate logistic regression analysis was performed. A p-value of <0.05 was considered statistically significant for all analyses.

RESULTS

A total of 1,041 women were evaluated in this study. Participants were divided into two groups based on the indication for oocyte cryopreservation: the donor group (n=590) consisted of healthy volunteers who froze their oocytes for donation purposes; the social group (n=451) included women who aimed to preserve their fertility due to advancing age.

Table 1 compares the donor and social groups in terms of information sources, educational level, income status, employment status, and payment methods for treatment expenses. A significant difference was found between the groups regarding sources of information ($p<0.001$). The majority of social group participants (89.3%) received information from obstetricians/gynecologists, while the most common sources in the donor group were media/social media (55.5%) and acquaintances/friends (39.1%). Participants informed through family physicians were only represented in the social group (2.6%). There was no significant difference between the groups in terms of educational level ($p=0.500$). In both groups, the majority of participants were university graduates (donor group: 86.1%; social group: 83.5%). Income status showed a marked difference between the groups ($p<0.001$). In the donor group, 32.8% reported no income, and 58.9% reported earning at the minimum wage level. In contrast, 95.7% of the social group had incomes above the minimum wage.

Employment status also differed significantly between the groups ($p<0.001$). While 97.3% of the social group were actively employed, this rate was 67.1% in the donor group. Among the donor group, 21.8% were unemployed, and 11% were students. The method of covering treatment expenses also varied significantly between the groups ($p<0.001$). In the donor group, all costs were covered by the recipient couple or the clinic. In the social group, 86.9% of participants financed the procedure themselves, while support from family (11.9%) and relatives (1.1%) was also reported. Table 2 presents a comparative analysis of the baseline demographic and clinical characteristics of participants in the donor and social groups. The mean age of participants in the donor group was significantly lower than that of the social group ($p<0.001$). Similarly, BMI was also found to be significantly lower in the donor group ($p<0.001$). In terms of ovarian reserve parameters, the donor group had significantly lower baseline FSH levels ($p<0.001$), while their AMH levels and antral follicle

Table 1. Motivators and sociodemographic characteristics of participants according to group

Variable	Donor group (n=590)	Social group (n=451)	*p* value
Source of information			
General practitioner	0 (0.0%)	12 (2.6%)	<0.001
Oncologist	0 (0.0%)	0 (0.0%)	–
Gynecologist	31 (5.3%)	403 (89.3%)	<0.001
Acquaintance/friend	231 (39.1%)	19 (4.2%)	
Media/social networks	328 (55.5%)	17 (3.7%)	
Education level			0.500
Primary school	6 (1.0%)	5 (1.1%)	
High school	76 (12.8%)	69 (15.2%)	
University	508 (86.1%)	377 (83.5%)	
Income level			<0.001
None	194 (32.8%)	11 (2.4%)	
Minimum legal wage	348 (58.9%)	8 (1.7%)	
Higher than minimum wage	48 (8.1%)	432 (95.7%)	
Employment status			<0.001
Unemployed	129 (21.8%)	5 (1.1%)	
Student	65 (11.0%)	7 (1.5%)	
Employed	396 (67.1%)	439 (97.3%)	
Expense coverage			<0.001
Recipient	590 (100%)	–	
Self	–	392 (86.9%)	
Parents	–	54 (11.9%)	
Relatives	–	5 (1.1%)	

Categorical variables were compared using the chi-square test or Fisher's exact test where appropriate. A p-value <0.05 was considered statistically significant.

counts were significantly higher ($p<0.001$), indicating a more favorable ovarian reserve profile compared to the social group.

The total gonadotropin dose used during ovarian stimulation was significantly lower in the donor group ($p<0.001$). The proportion of cycles initiated with a random-start protocol was comparable between the two groups ($p=0.230$). However, a significant difference was observed in the types of stimulation protocols employed ($p=0.002$). While the most commonly used regimen in both groups was the short antagonist protocol, the progesterone-primed protocol was more frequently used in the social group (12.4% vs. 6.4%). Trigger methods for ovulation also differed significantly between groups ($p<0.001$); human chorionic gonadotrophin (hCG) was predominantly used in the donor group, whereas agonist and especially dual trigger protocols were more frequently employed in the social group. Notably, the dual trigger method was exclusively used in the social group 7.9% vs. 0% in the donor group.

Table 3 summarizes the findings related to oocyte yield in the donor and social groups. A comparison between the groups revealed that oocyte retrieval was predominantly performed in a single attempt in the donor group (95.4%), whereas this rate was significantly lower in the social group (78.0%), with a higher frequency of second retrieval cycles observed (19.5%) ($p<0.001$). Dual stimulation protocols were applied in 2.4% of the social group, while no such cases were recorded in the donor group. The mean number of oocytes retrieved per patient was significantly higher in the donor group ($p<0.001$). Similarly, the proportion of patients with more than 15 oocytes retrieved per cycle was markedly higher in the donor group ($p<0.001$). Both the number of mature MII oocytes ($p<0.001$) and immature oocytes ($p<0.001$) were significantly greater in the donor group compared to the social group. The cumulative number of vitrified oocytes was also substantially higher in the donor group, with an average of 23.0 oocytes per patient, compared to 4.7 in the social group ($p<0.001$).

Table 2. Baseline characteristics of participants

Variable	Donor group (n=590)	Social group (n=451)	*p* value
Age (years)	24.8±3.3	34.4±6.9	<0.001
BMI (kg/m²)	21.5±5.1	24.1±3.4	<0.001
FSH (mIU/mL)	7.5±3.9	11.8±4.6	<0.001
AMH (ng/mL)	2.7±3.7	0.6±0.6	<0.001
Baseline antral follicle count	8.7±5.4	5.1±2.8	<0.001
Total dose of stimulation (IU)	1516±315	325±1047	<0.001
Random start (n, %)	19 (3.2%)	21 (4.6%)	0.230
Stimulation protocol			0.002[1]
Short antagonist	519 (87.9%)	410 (90.1%)	
Progesterone-primed	38 (6.4%)	56 (12.4%)	
Long agonist	33 (5.5%)	15 (3.3%)	
Ovulation trigger			<0.001[2]
hCG	521 (88.3%)	343 (76%)	
Agonist trigger	69 (11.6%)	72 (16%)	
Double trigger	–	36 (7.9%)	

[1]Chi-square test for multiple group comparison within stimulation protocols.
[2]Chi-square test for multiple group comparison within ovulation trigger methods.
All continuous variables were analyzed using independent samples t-test and categorical variables were analyzed using chi-square test.
BMI: Body mass index, FSH: Follicle stimulating hormone, AMH: Anti-Müllerian hormone, IU: International unit, hCG: Human chorionic gonadotrophin

Table 3. Oocyte yield of the groups

Variable	Donor group (n=590)	Social group (n=451)	*p* value
Oocyte pick-up - once	563 (95.4%)	352 (78.0%)	<0.001
Oocyte pick-up - twice	27 (4.5%)	88 (19.5%)	
Oocyte pick-up - double stimulation	0 (0.0%)	11 (2.4%)	
Number of oocytes retrieved/patient	39.5±19.7	5.0±4.8	<0.001
>15 oocytes retrieved/cycle	544 (92.2%)	19 (4.2%)	<0.001
Number of mature oocytes/patient	30.4±16.3	4.3±4.4	<0.001
Number of immature oocytes/patient	3.3±2.8	0.4±0.7	<0.001
Cumulative number of oocytes vitrified	23.0±14.4	4.7±4.8	<0.001
Ovarian hyperstimulation syndrome	87 (14.7%)	6 (1.3%)	<0.001

Moreover, the incidence of OHSS was significantly higher in the donor group ($p<0.001$).

DISCUSSION

In the present study, individuals who underwent oocyte cryopreservation were categorized into two groups, donor and social groups, and compared. Significant differences were observed between the groups in terms of sociodemographic characteristics, biological parameters, ovarian stimulation response, and oocyte yield. The findings indicate that the two groups differed not only clinically but also in terms of motivation and socioeconomic status.

The majority of participants in the donor group were low-income, unemployed or students, and all treatment expenses were covered by the egg-donation recipients. These factors strongly suggest that the primary motivation for participation in the donor group was financial. This is consistent with previous reports indicating that oocyte donors often engage in donation primarily for economic reasons rather than altruism.[7,8] Although the donor group had a slightly higher rate of university education than the social group, the social group differed in terms of employment and having a higher income, suggesting that these were career-oriented women making informed, elective decisions to postpone childbearing.

Furthermore, the fact that most of these individuals obtained information directly from gynecologists reflects a high level of medical awareness. These findings again align with the existing literature suggesting that increasing educational attainment and professional aspirations are driving women to delay reproduction and opt for elective fertility preservation.[9,10]

Significant differences were also observed in biological parameters, such as age, BMI, hormone profiles, and ovarian reserve. Donors were almost 10 years younger on average than the social group participants. Donors are typically young women with high fertility potential, and most studies report oocyte donors to be within the 20-30 years old age range.[7] Age also impacts BMI and hormone levels. The donor group had a significantly lower mean BMI than the social group but both were in the normal weight range. A lower BMI is generally preferred in donor selection and is associated with better ovarian reserve.[11]

The significantly higher mean FSH and lower AMH levels in the social group reflect an age-related decline in ovarian reserve.[12] Similarly, the antral follicle count was significantly lower in the social group. Antral follicle count is a widely accepted biomarker for predicting ovarian response and is expected to be higher in younger individuals. These biological differences influenced stimulation strategies. The mean total gonadotropin dose was significantly higher in the social group than in the donor group, reflecting an effort to compensate for diminished ovarian reserve.[13]

Although the short antagonist protocol was the most commonly used stimulation method in both groups, a progesterone-primed ovarian stimulation (PPOS) protocol was more frequently used in the social group. PPOS is favored in fertility preservation for its flexibility in cycle scheduling.[14]

The random-start protocol also tended to be more common in the social group, though not significantly so. This protocol is widely adopted in time-sensitive indications, such as fertility preservation for cancer patients.[15] Trigger methods for ovulation also differed significantly between groups, with hCG predominantly being used in the donor group, whereas agonist or dual-trigger methods were more frequently employed in the social group to minimize OHSS risk.[16] In terms of oocyte yield, the donor group demonstrated a superior quantitative and qualitative response. A single stimulation cycle was sufficient for 95.4% of donors, while 19.5% of the social group required a second cycle, and 2.4% underwent dual stimulation. Dual stimulation is considered effective for patients with limited time and diminished ovarian reserve.[17,18] The average number of retrieved oocytes was also significantly higher in the donor group. Furthermore, the proportion of cycles yielding ≥15 oocytes was more than 90% in the donor group versus <5% in the social group. These differences are attributed to variations in age, ovarian reserve, and stimulation protocols.[19,20]

The number of mature oocytes MII was also significantly higher in the donor group compared to the social group. Although the donor group also had a significantly higher number of immature oocytes, this is likely due to the overall higher oocyte yield. A greater number of mature oocytes provides a distinct advantage for fertilization and embryo development.

Similarly, the mean number of vitrified oocytes was significantly greater in the donor group, indicating that younger women with better ovarian reserve exhibit a better response to stimulation.[21]

The significantly higher incidence of OHSS observed in the donor group compared to the social oocyte cryopreservation group highlights a notable clinical concern. This increased risk (approximately 14% vs approximately 1%) is likely attributable to the higher ovarian reserve typically observed in donors, the more robust ovarian response to stimulation, and the prevalent use of hCG for triggering final oocyte maturation in this group. In contrast, the social group generally demonstrated a more attenuated ovarian response, and protocols incorporating gonadotropin releasing hormone (GnRH) agonist or dual triggering were more frequently employed, both of which are recognized strategies for reducing OHSS risk.[22] In the literature, OHSS incidence in oocyte donors undergoing hCG-triggered protocols has been reported to range between 17% and 30%, which is higher than the 14.7% incidence found in our donor cohort.[23] The selection of trigger agent and stimulation protocol plays a critical role in OHSS pathogenesis.[22,24] Given the typically diminished ovarian reserve in social oocyte cryopreservation patients, the risk of OHSS in this population is inherently lower.[25] This corresponds well with our finding of a 1.3% OHSS incidence in the social group. Systematic reviews and clinical studies have shown that GnRH agonist triggering is associated with a significantly lower risk of OHSS compared to hCG, particularly in antagonist protocols.

Therefore, in high responders such as oocyte donors, the use of GnRH agonist triggering, cycle segmentation strategies, and close patient monitoring are strongly recommended.[22,24]

However, reports exist of OHSS development even after GnRH agonist triggering, particularly in young women with very high oocyte yield, suggesting that no approach is entirely risk-free.[26] Given the potential severity of OHSS, including hospitalization, thromboembolic events, and long-term reproductive complications, mitigating this risk is paramount. Severe OHSS can result in life-threatening complications, such as deep vein thrombosis, acute renal failure, and acute respiratory distress syndrome, with some studies reporting a 4.4% rate of such outcomes.[27] Moreover, OHSS has been associated with adverse obstetric outcomes, including low birth weight and preterm delivery.[28] Therefore, careful monitoring of ovarian response during stimulation, individualized protocols, and the use of preventive strategies, such as GnRH agonist triggering and freeze-all approaches, should be strongly considered, especially in high responders.[29] Close follow-up, timely recognition of symptoms, and proactive management can significantly reduce the clinical burden of OHSS and improve patient safety, as supported by prospective protocols such as stop OHSS.[29]

Study Limitations

This study's strengths include a large sample size and comprehensive evaluation of sociodemographic and biological factors across donor and social oocyte cryopreservation groups. Limitations include its retrospective design, reliance on patient records without standardized questionnaires, and lack of adjustment for potential confounders such as age, BMI, and AMH.

CONCLUSION

In conclusion, this study comprehensively investigated the socioeconomic, biological, and clinical disparities between donor and social oocyte cryopreservation groups in a Turkish population and highlights the need for individualized treatment strategies in fertility preservation. Donors were typically young women with high ovarian reserve and financially motivated participation, whereas the social group comprised older, highly educated, career-oriented women making elective reproductive choices. Recognizing these distinctions in clinical practice may enhance patient counseling and optimize treatment outcomes. Moreover, in light of the growing demand for elective fertility preservation, the findings of this study may help inform evidence-based decision-making regarding fertility planning and resource allocation. In this context, the increased OHSS risk observed among donors underscores the importance of vigilant clinical follow-up and the implementation of safer stimulation and triggering strategies. The study was conducted to provide guidance for clinical practice and establish a foundation for future research in the field of fertility preservation.

Ethics

Ethics Committee Approval: Ethical approval for this study was granted by the Ethics Committee of Bolu Abant İzzet Baysal Faculty of Medicine (approval number: 2025/340, date: 21.07.2025).

Informed Consent: This study was a retrospective cohort analysis.

Authorship Contributions

Surgical and Medical Practices: N.E.A., Y.İ., H.U.Ş., Concept: Y.İ., Ö.D.S., Design: N.E.A., Ö.D.S., Data Collection or Processing: Y.İ., H.U.Ş., Analysis or Interpretation: N.E.A., Ö.D.S., Literature Search: Y.İ., H.U.Ş., Writing: N.E.A., Ö.D.S.

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Case Report

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Giant Ovarian Fibrothecoma in a Postmenopausal Woman Mimicking Malignancy with Bilateral Hydronephrosis: A Case Report

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ABSTRACT

Sex cord-stromal tumors (SCSTs) are rare ovarian neoplasms accounting for less than 5% of all ovarian tumors. This case report presents a 59-year-old postmenopausal woman with a giant ovarian fibro-thecoma presenting with abdominal pain, distention, pelvic heaviness, and mild hematuria. Radiological investigations revealed a large adnexal mass causing bilateral hydronephrosis. Surgical management included total hysterectomy with bilateral salpingeo-oophorectomy, and final pathology confirmed a benign fibro-thecoma. This case highlights diagnostic and therapeutic considerations in managing large ovarian SCSTs in postmenopausal women.

Keywords: Sex cord-stromal tumor, fibro-thecoma, ovarian neoplasm, postmenopausal, hydronephrosis, ovarian mass

INTRODUCTION

Sex cord-stromal tumors (SCSTs) are a rare group of ovarian neoplasms accounting for approximately 5-8% of all ovarian tumors.[1] Among them, fibrothecomas represent a subtype that lies along a histological spectrum between fibromas and thecomas, containing both fibroblastic and thecal elements.[2,3] These tumors are typically benign and often asymptomatic or incidentally discovered. However, in rare instances, they can grow to considerable sizes and exhibit imaging features that closely mimic malignant ovarian neoplasms.[4,5]

The current case is notable for a giant ovarian fibrothecoma presenting with bilateral hydronephrosis, an uncommon complication resulting from ureteral compression.[6,7] The large size of the tumor and complex imaging characteristics initially raised concern about malignancy, leading to extensive surgical planning. Furthermore, renal function was compromised due to obstructive uropathy, adding urgency and complexity to the case.

This report highlights the diagnostic dilemma posed by such tumors, the importance of careful preoperative evaluation, and the value of intraoperative frozen section analysis in guiding surgical decision-making.[8,9] By highlighting these challenges, this case contributes to the limited literature on fibrothecomas presenting with hydronephrosis and serves as an important lesson in avoiding overtreatment in similar clinical scenarios.

CASE REPORT

A 59-year-old postmenopausal woman presented with a 3-month history of progressive right flank and lower abdominal pain, accompanied by gradual abdominal distention and gross hematuria, which she reported as visible blood in the urine. Urinalysis confirmed gross hematuria, revealing >50 red blood cells per high-power field.

Her medical history was unremarkable, except for a ureteroscopic laser lithotripsy performed 12 years prior for nephrolithiasis. She denied any recent urinary tract infections, weight loss, or systemic symptoms.

On physical examination, she had abdominal distention, right-sided tenderness, and a palpable firm pelvic-abdominal mass extending above the pelvis.

Initial imaging with transabdominal ultrasound revealed a large right adnexal mass measuring approximately 14 × 12 × 8.5 cm, extending to the level of the umbilicus. This prompted further evaluation with magnetic resonance imaging, which demonstrated a heterogeneous, well-circumscribed, complex mass causing compression of both ureters, resulting in bilateral hydronephrosis Figure 1. These features raised strong radiological suspicion for an invasive or borderline ovarian malignancy.

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Laboratory investigations revealed normal tumor markers, including CA-125 and CA 19-9, but renal function was impaired, with a serum creatinine of 1.8 mg/dL and eGFR of 35 mL/min/1.73 m^2, likely due to obstructive uropathy.

In view of bilateral hydronephrosis and impaired renal function, bilateral double-J (DJ) ureteral stents were placed preoperatively to relieve ureteral obstruction and preserve kidney function.

Following stabilization, the patient underwent elective exploratory laparotomy via midline incision. Peritoneal fluid was aspirated and sent for cytology. Intra-operatively, a large solid mass originating from the right ovary was identified. En-bloc excision of the mass with the right adnexa was performed, along with total abdominal hysterectomy and left adnexectomy.

A frozen section analysis of the mass indicated a benign stromal tumor with no features of malignancy. Based on this intraoperative finding, no omentectomy or lymphadenectomy was performed. The final procedure completed was a total abdominal hysterectomy with bilateral salpingeo-oophorectomy.

Pathological Findings

Grossly, the tumor measured 13 × 10 cm, was solid, and encapsulated Figure 2. Histopathology confirmed a fibro-thecoma with spindle-shaped fibroblastic and thecal-like cells in a collagenous matrix. The tumor stained positive for inhibin, calretinin, and vimentin, supporting the diagnosis of fibrothecoma. No atypia or mitotic activity was found. All other tissues examined were benign.

Cytology

Peritoneal fluid was negative for malignancy and showed reactive mesothelial cells with inflammatory cells and histiocytes.

Postoperative Course

Creatinine improved from 1.8 to 1.1 mg/dL by postoperative day 7.

eGFR: 35 mL/min/1.73 m^2 pre-op → 68 mL/min/1.73 m^2 post-op.

DJ stents removed after 4 weeks; no hydronephrosis on ultrasound at 3 months.

Patient asymptomatic at 6-month follow-up.

The patient's symptoms resolved, and renal function improved postoperatively. She was discharged on postoperative day four in good condition.

DISCUSSION

Fibrothecomas are benign SCSTs of the ovary, most commonly seen in peri- and post-menopausal women.[10,11] They represent a spectrum between fibromas and thecomas, with varying proportions of fibroblastic and thecal cells.[12] While many are small and asymptomatic[13], larger tumors may present with nonspecific abdominal or pelvic symptoms due to mass effect[14], such as pressure on the bladder or ureters, occasionally leading to hydronephrosis.[15]

Some fibrothecomas may produce estrogen[16], potentially leading to endometrial hyperplasia or abnormal uterine bleeding, particularly in postmenopausal women.[17]

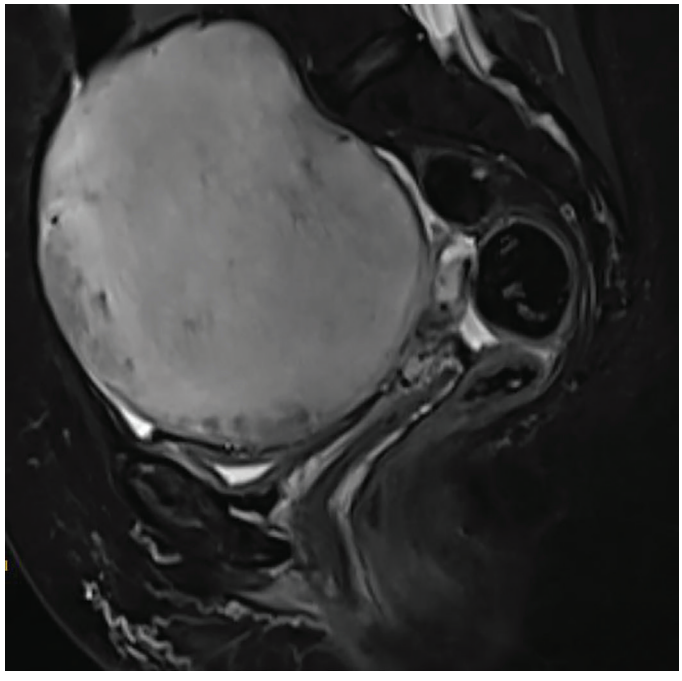

Figure 1. Preoperative MRI showing the large adnexal mass
MRI: Magnetic resonance imaging

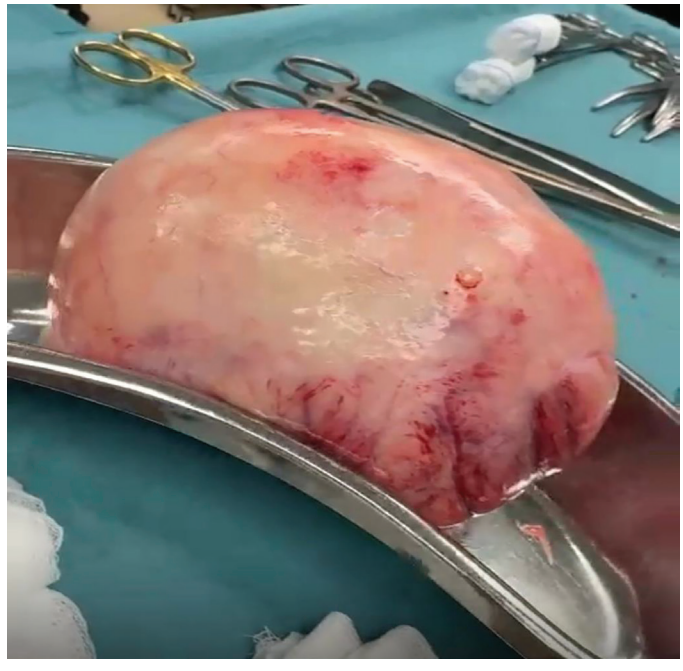

Figure 2. Intraoperative photo of the excised ovarian mass

In the present case, no hormonal symptoms or endometrial pathology were noted.

Imaging findings may be misleading, especially in large tumors with solid components or degenerative changes, raising suspicion for malignancy. As tumor markers, such as CA-125, are often non-specific or within normal limits in such cases[18,19], they are not reliable for diagnosis. Therefore, surgical exploration is often necessary when imaging suggests a complex adnexal mass.

Frozen section during surgery may provide valuable intraoperative guidance, as in the presented case.[20,21] In benign tumors, especially in postmenopausal women, total hysterectomy with bilateral salpingeo-oophorectomy is the standard approach.[22,23] Conservative surgery may be considered in younger patients with fertility concerns.[24,25]

This case highlights the need for a broad differential when evaluating complex adnexal masses and the importance of integrating clinical[26], radiological, intraoperative, and histological data in guiding management, and highlights the value of intraoperative histopathology to potentially avoid unnecessary extensive surgery.

CONCLUSION

This case highlights the importance of a multidisciplinary approach in the management of large adnexal masses in postmenopausal women. The combination of imaging, tumor markers, intraoperative frozen section, and histopathology facilitated optimal care. Avoidance of unnecessary radical surgery in a benign case preserved quality of life without compromising patient safety.

Ethics

Informed Consent: Informed consent was obtained from the patient for the publication of this case report and any accompanying images.

Authorship Contributions

Surgical and Medical Practices: A.E.M.A.S., N.R.H.A., M.A., W.H., Concept: A.E.M.A.S., N.R.H.A., M.A., W.H., Design: A.E.M.A.S., N.R.H.A., M.A., W.H., Data Collection or Processing: A.E.M.A.S., N.R.H.A., M.A., W.H., Analysis or Interpretation: A.E.M.A.S., N.R.H.A., M.A., W.H., Literature Search: A.E.M.A.S., N.R.H.A., M.A., W.H., Writing: A.E.M.A.S., N.R.H.A., M.A., W.H.

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Case Report

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Fatal Retroperitoneal Hemorrhage in Pregnancy due to Screw-Related Vascular Injury After Kyphoscoliosis Surgery

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ABSTRACT

This case report presents a fatal maternal complication that occurred three years after kyphoscoliosis surgery in a 27-year-old primigravida. At 33 weeks of her first pregnancy, the patient developed a massive retroperitoneal hemorrhage secondary to spontaneous vascular injury caused by protruding pedicle screws from prior posterior spinal instrumentation. The increased intra-abdominal pressure and progressive uterine expansion during advanced pregnancy are thought to have exacerbated contact between the screw tips and the iliac vessels, eventually extending to the abdominal aorta. This catastrophic vascular injury precipitated a large retroperitoneal hematoma and subsequently triggered placental abruption, culminating in maternal mortality despite emergency surgical intervention. To the best of our knowledge, this represents a rare but critical obstetric complication in women with a history of complex spinal instrumentation. The case emphasizes the need for careful multidisciplinary prenatal surveillance, pre-delivery imaging of vascular and implant relationships, avoidance of excessive uterine pressure during delivery, and heightened awareness of screw-related vascular risks during pregnancy and cesarean planning.

Keywords: Congenital kyphoscoliosis, spinal instrumentation, screw-related vascular injury, pregnancy, cesarean

INTRODUCTION

Congenital kyphoscoliosis is a complex spinal deformity that is typically diagnosed in childhood or adolescence and is often surgically treated with posterior spinal fusion or instrumentation. These surgeries may permanently alter retroperitoneal and pelvic vascular anatomy.[1] Pregnancy in such patients poses both mechanical and systemic challenges, including reduced respiratory capacity, pain management difficulties, and complex delivery planning. Literature indicates a higher rate of Cesarean deliveries in such patients, although serious vascular complications are rarely reported.[2] This report discusses a fatal vascular injury in the third trimester of pregnancy and offers insights into the management of similar cases.

CASE REPORT

A 27-year-old primigravida at 33+2 weeks of gestation presented with complaints of hematemesis, chills, and constipation. She had a known history of congenital kyphoscoliosis and thoracolumbar spinal instrumentation. Her body mass index was 35 kg/m^2 with no history of hypertension or diabetes. On admission, her vital signs were stable. Her hemoglobin level dropped from 9.2 to 8.6 g/dL during follow-up. NST was reactive, and BPP score was 8/8. Gastrointestinal bleeding was initially suspected. However, due to worsening abdominal pain and hemoglobin drop, an obstetric evaluation was performed with suspicion of placental abruption. Pelvic magnetic resonance imaging (MRI) revealed a retroperitoneal hematoma extending to the mediastinum, with normal placental structures. While preparing for surgery, the patient's condition deteriorated, and fetal bradycardia developed, prompting an emergency cesarean section (CS) (Figures 1, 2).

Intraoperative Findings

A CS was performed under general anesthesia. A 2200 g female infant was delivered (Apgar 3/7). Placental abruption was noted in approximately 50% of the placenta. While closing the uterus, a hematoma extending from the pelvis to the mediastinum was identified in the retroperitoneal space. Vascular surgery consultation was obtained. Dissection revealed a partial avulsion and arterial bleeding extending from the external iliac vein to the abdominal aorta. Despite vascular clamping, ligation, and surgical repair, bleeding could not be

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controlled. The patient received 5 units of RBC, 4 units of FFP, and 6 units of cell-saver blood. Despite resuscitation efforts, the patient suffered three cardiac arrests and was eventually declared deceased (Figures 3-5).

DISCUSSION

This case underscores how spinal deformities and previous surgeries can alter pelvic vascular anatomy, leading to life-threatening complications during pregnancy. Retroperitoneal hemorrhage in our patient was most likely provoked by screw-related vascular injury exacerbated by the gravid uterus. Imaging plays a pivotal role in diagnosis and preoperative planning. MRI is the preferred modality in pregnancy due to the absence of ionizing radiation and its ability to provide detailed soft tissue and vascular evaluation. However, MRI is limited by susceptibility artifacts created by metallic implants, which can obscure fine details. CT, in contrast, offers superior visualization of bony structures and implant positioning but involves ionizing radiation, which poses potential fetal risks and therefore is less desirable during pregnancy.[3,4]

From an obstetric perspective, excessive fundal pressure, such as the Kristeller maneuver, should be strictly avoided in patients with spinal instrumentation due to the potential risk of exacerbating vascular compression and screw-related injury. Similarly, care must be taken to avoid undue uterine compression during cesarean delivery and fetal extraction, as increased intra-abdominal pressure may directly aggravate vascular contact with implants.[5]

This case highlights the importance of pre-delivery pelvic imaging in women with prior kyphoscoliosis surgery and posterior spinal instrumentation. Delivery should ideally be planned with a multidisciplinary team including obstetrics, perinatology, radiology, vascular surgery, and anesthesiology.

Figure 1. Coronal pelvic MRI demonstrating a large retroperitoneal hematoma extending cranially towards the mediastinum. The gravid uterus is displaced superiorly, and hematoma formation is visible adjacent to the vascular and spinal structures

MRI: Magnetic resonance imaging

Figure 2. Sagittal cervical-thoracic MRI showing posterior spinal instrumentation and altered vertebral alignment in a patient with congenital kyphoscoliosis. The presence of metallic screws causes susceptibility artifacts, partially obscuring visualization

MRI: Magnetic resonance imaging

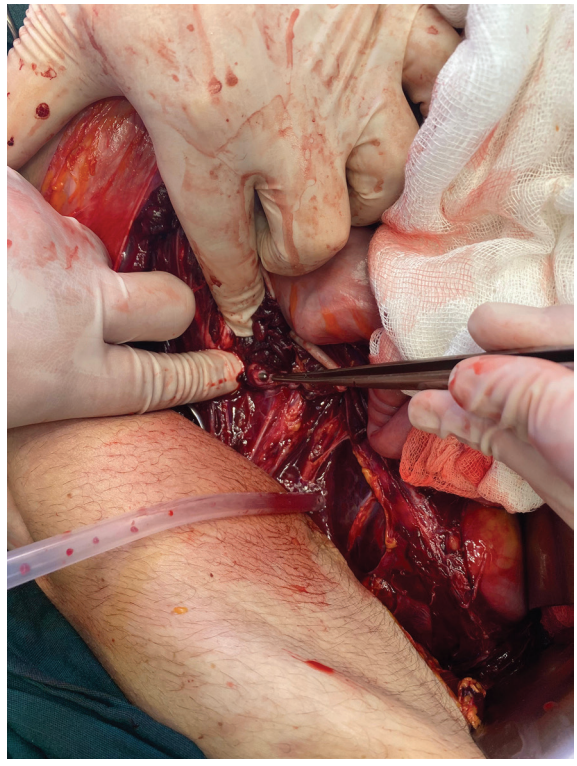

Figure 3. Intraoperative photograph during cesarean section showing protrusion of spinal instrumentation screws into the abdominal cavity in a patient with a history of kyphoscoliosis surgery

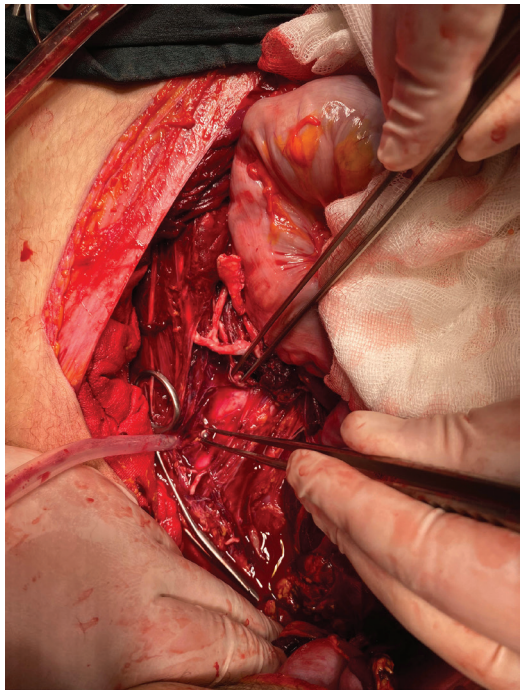

Figure 4. Surgical exploration demonstrating screw penetration in close proximity to the iliac vessels, contributing to retroperitoneal hematoma formation

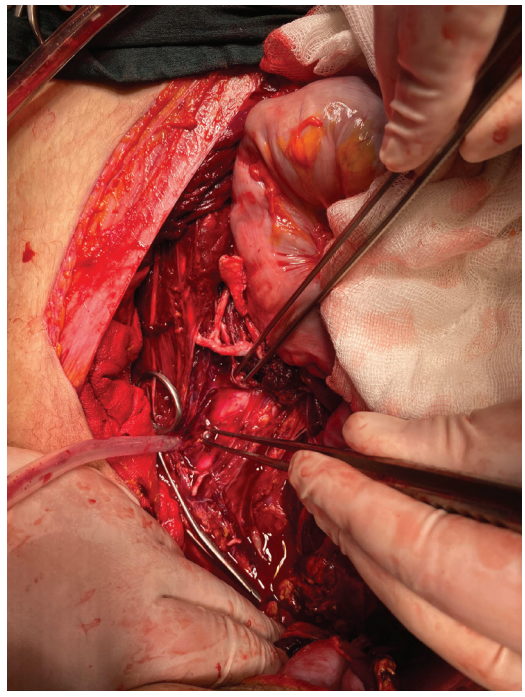

Figure 5. Intraoperative view revealing extensive vascular injury involving the iliac arteries and abdominal aorta caused by protruding pedicle screws, which subsequently triggered retroplacental hematoma and placental abruption

Ethics

Informed Consent: Written informed consent was obtained from the patient's family for publication of this case report and accompanying images.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.A., H.U., S.B., S.S.A., M.A.K., Concept: S.A., M.A.K., Design: S.A., Data Collection or Processing: S.A., H.U., S.B., S.Ö.Y., Analysis or Interpretation: S.A., Literature Search: S.A., H.U., S.Ö.Y., Writing: S.A., H.U.

Conflict of Interest: The authors declare that they have no conflict of interest.

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Letter to the Editor

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Hundreds of Surgeries or Hundreds of Citations? Rethinking Surgical Excellence

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Keywords: Surgical excellence, academia, clinical competence, publications

INTRODUCTION

The field of surgery stands at a critical juncture. While scientific productivity has reached unprecedented levels, concerns are growing that the core foundation of surgical expertise, practical experience in the operating room, is being increasingly marginalized. Academic success, often measured by the quantity of publications and citation metrics, is now frequently prioritized over technical mastery and clinical judgment. This shift demands urgent reflection from the surgical profession.

The Rise of Publication Metrics in Surgical Careers

In recent decades, academic medicine has embraced a culture where quantitative research metrics, including h-indices, impact factors, and citation counts, serve as major indicators of professional success.[1,2] While these metrics offer standardized ways to assess scholarly influence, their dominance in promotion criteria risks overshadowing clinical competence. For surgeons, whose primary duty lies in the precise and skilled care of patients, this imbalance is particularly concerning. Today, young surgical trainees are often encouraged to author multiple papers early in their careers, sometimes even on procedures they have performed only rarely or not at all.[3] Authorship, even without significant clinical experience, is increasingly seen as a prerequisite for fellowship acceptance, academic appointments, and career advancement. This trend may foster a generation of surgeons whose resumes are rich with publications but less reflective of hands-on surgical proficiency. While the emphasis on academic publishing has grown, it is important to acknowledge that research involvement can offer real benefits to surgical trainees. Participation in research activities can enhance critical thinking, promote evidence-based practice, and provide exposure to innovation. Studies have shown that research experience is increasingly valued in surgical residency and fellowship applications, and that many projects, such as case series, quality improvement initiatives, and surgical audits, are directly rooted in patient care.[4,5]

Surgical mastery is inherently experiential. It is cultivated through repetition, mentorship, management of complications, and the disciplined refinement of technique. No number of publications can substitute for the judgment honed under real operative conditions or the tacit knowledge acquired through tactile engagement with human anatomy. Research from Ericsson et al.[6] on deliberate practice underscores that true expertise in any field, including surgery, requires sustained, focused, and feedback-driven experience over years, not merely theoretical knowledge. In surgery, the consequences of inadequate technical proficiency are profound, potentially impacting patient safety and outcomes.

The Influence of Artificial Intelligence

The emergence of artificial intelligence (AI) has further influenced academic productivity by streamlining data analysis, generating draft manuscripts, and aiding in literature synthesis.[7] While AI offers significant efficiency gains, it may also contribute to a surge of publications that are detached from operative experience, amplifying the existing disconnect between research output and clinical skill development.

Recalibrating Surgical Values

The profession must urgently recall what it values most in its members. Scientific contributions remain vital. Advances in surgical techniques, patient safety protocols, and healthcare policy depend on rigorous academic inquiry. However,

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research excellence must complement, not replace, technical mastery (Figure 1). Current efforts to reform surgical education, such as competency-based training models, underscore the importance of real-world skill acquisition over time-based or publication-based advancement.[8] Accreditation bodies and academic institutions must continue to prioritize operative experience, technical assessment, and clinical outcomes when evaluating surgical trainees and faculty. Moreover, career advancement criteria should recognize and reward excellence in teaching, mentorship, surgical innovation, and clinical leadership alongside traditional research productivity.

The Patient Perspective

At the critical moment when a patient is entrusted to a surgeon's care, it is the surgeon's clinical judgment, technical precision, and prior hands-on experience, rather than their publication record, that most directly influence outcomes.

Figure 1. Balancing surgical excellence: scientific publications vs. surgical experience. A conceptual illustration depicting a balance scale, with one side representing scientific publications (symbolized by a stack of academic papers) and the other side representing surgical experience (symbolized by a hand holding a scalpel). The image underscores the need for balance between academic productivity and operative skill in defining modern surgical excellence.

CONCLUSION

The dichotomy between hundreds of surgeries and hundreds of citations is a false one: both scholarship and skill are essential to the future of surgery. Yet, in the current academic climate, it is imperative to restore balance. Surgical excellence cannot be measured by bibliometric indices alone. It must be reflected in a surgeon's ability to heal, to act decisively in critical moments, and to deliver safe, compassionate care. As a profession, we must ensure that the next generation of surgeons is celebrated not only for their contributions to literature but, more importantly, for the lives they save or transform through their surgical craft.

Footnotes

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