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Metabolic Dysregulation in Women with Unexplained Infertility and Pregnancy Loss

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Abstract

This prospective cohort study investigates the association between metabolic disturbances and reproductive dysfunction in women with idiopathic infertility and recurrent pregnancy loss (RPL). Conducted at the Perinatal Centre of Grozny from 2022 to 2025, the study involved 240 women allocated into three groups: Group 1 (n=120) with idiopathic infertility/RPL, Group 2 (n=60) with tubal factor infertility, and a control Group 3 (n=60) of fertile women. All participants underwent a comprehensive assessment, including anthropometric measurements, hormonal profiling, evaluation of insulin resistance (HOMA-IR, QUICKI), adipokine status (leptin, adiponectin), oxidative stress markers (MDA, SOD), and transvaginal ultrasonography. The results revealed a distinct metabolic phenotype in Group 1, characterized by significantly higher BMI, waist circumference, and markers of insulin resistance (HOMA-IR: 3.8 vs. 1.4 in controls, $p<0.001$). Profound adipokine dysregulation was evident, with a leptin/adiponectin ratio exceeding 4.95 compared to 1.10 in Group 3 ($p<0.001$). Concurrently, elevated oxidative stress was observed (MDA: 6.85 nmol/mL vs. 4.55, $p<0.001$). These metabolic alterations correlated with impaired reproductive markers, including a higher LH/FSH ratio, hyperandrogenemia, reduced antral follicle count, and significantly poorer endometrial receptivity (endometrial thickness: 8.1 mm vs. 10.2 mm; three-line endometrium incidence: 56.7% vs. 95.0%). In contrast, Group 2 parameters aligned with healthy controls. The findings strongly suggest that insulin resistance, adipokine imbalance, and oxidative stress are integral pathophysiological components of idiopathic infertility and RPL, advocating for their recognition as a "metabolic" subtype of reproductive failure. Integrating metabolic screening into standard diagnostic protocols is crucial for targeted preconception management.

Keywords: Idiopathic infertility, Recurrent pregnancy loss, Insulin resistance, Adipokines, Oxidative stress, Endometrial receptivity

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Introduction

The reproductive health of the human population in the 21st century is under the cross-pressure of two global trends: demographic ageing and a parallel epidemic of metabolic disorders (Weitekamp *et al*., 2021). The intricate interplay between metabolic homeostasis and reproductive function has become a focal point of modern reproductive medicine (Chadchan *et al*., 2022). While energy deficit has long been recognised as a potent inhibitor of fertility, compelling evidence now confirms that energy excess and its associated metabolic disruptions – namely, insulin resistance, adipose tissue dysfunction, and chronic inflammation – constitute an equally powerful barrier to successful conception and gestation (Barbouni *et al*., 2025; Barraza-Ortega *et al*., 2025; Sasikala *et al*., 2026). These disturbances form a vicious cycle that impairs the hypothalamic-pituitary-ovarian axis, compromises oocyte quality, diminishes endometrial receptivity, and ultimately manifests as clinical outcomes such as anovulatory infertility and recurrent pregnancy loss (Chen *et al*., 2022; Potiris *et al*., 2024; Valera *et al*., 2025).

The escalating prevalence of key metabolic and reproductive pathologies over recent decades underscores the magnitude of this public health challenge, revealing a worrying synchronicity that suggests a deep-seated pathogenic connection (Szlapinski & Hill, 2021). The dynamic progression of these conditions is clearly illustrated by the epidemiological data presented in **Table 1**, which summarises the trends across three distinct periods from 1980 to the present day. This tabulated data demonstrates a synchronous rise in the rates of obesity, insulin resistance, and infertility, moving in tandem over time (Yong *et al*., 2023; Kong *et al*., 2024).

For instance, the prevalence of obesity among women of reproductive age has surged from approximately 8-10% in the 1980-2000 period to an estimated 25-30% in recent years, while the rate of infertility in couples has concurrently increased from 8-10% to 15-17% (Arıkan & Sagsoz, 2023). This parallel growth strongly implies that the connection is not merely coincidental but rather indicative of shared underlying pathophysiological mechanisms, necessitating a thorough and integrated investigation (Li *et al*., 2024).

Table 1. Dynamics of the Prevalence of Metabolic and Reproductive Disorders Among Women of Reproductive Age in Different Time Periods.

Pathology / Parameter	Period 1980-2000	Period 2000-2015	Period 2015-2025 (Estimates and Forecasts)
Obesity (BMI ≥30 kg/m²)	Steady increase from ~8-10% to ~12-15% in developed countries.	Accelerated growth to ~18-25% in developed countries; sharp increase in developing countries (~10-15%).	Stabilisation at a high level (~25-30%) in developed countries; continued growth in developing countries (~20%). Global pandemic.
Insulin Resistance and Type 2 Diabetes	Awareness of the problem. Increasing incidence of Type 2 Diabetes in women <40 years.	Clear link with obesity. Widespread diagnosis of insulin resistance in PCOS. Prevalence of prediabetes in women with obesity reaches 30-40%.	Focus on pre-disease forms. Use of sensitive markers (HOMA-IR, oral glucose tolerance test). The global prevalence of Type 2 Diabetes continues to rise.
Polycystic Ovary Syndrome (PCOS)	Prevalence ~5-7% according to NIH-1990 criteria.	Refinement of criteria (Rotterdam, 2003). Prevalence increased to ~10-15% considering new criteria. Understanding as a metabolic syndrome.	Prevalence stabilised at ~15-21%. In-depth study of phenotypes. Early diagnosis of metabolic risks in adolescents.
Infertility in Couples	~8-10%. Predominance of tubal factor.	Increase to ~12-15%. Increase in the proportion of endocrine (anovulatory) factors associated with obesity and PCOS.	Stabilisation at ~15-17%. Clear identification of 'metabolic' infertility as a distinct pathogenetic subtype.
Pregnancy Loss	Frequency ~15-20%. Idiopathic losses constituted a significant proportion.	Understanding the role of insulin resistance, thrombophilias, and subclinical hypothyroidism. Metabolic factor identified in 30-40% of cases.	Metabolic screening becomes a standard of examination. The proportion of idiopathic losses decreases due to the identification of metabolic causes.

The theoretical basis for understanding the presented statistics lies in complex molecular and cellular interactions. A key pathogenetic link is insulin resistance, a condition in which target cells (hepatocytes, adipocytes, myocytes) lose insulin sensitivity (Ahmed *et al*., 2021; Garg *et al*., 2023). Compensatory hyperinsulinaemia, arising in response to this, has a direct pathological effect on the ovaries (Zhao *et al*., 2023). Insulin, binding to insulin and IGF-1 receptors on theca cells, potentiates the action of luteinising hormone (LH), leading to the overproduction of androgens (Chen *et al*., 2023; Eng *et al*., 2024). Simultaneously, hyperinsulinaemia suppresses the synthesis of sex hormone-binding globulin (SHBG) in the liver, which increases the fraction of biologically active free androgens in the blood plasma (Bourebaba *et al*., 2023). Androgenisation of the ovaries disrupts the process of folliculogenesis, leading to atresia of antral follicles and the formation of cystic-atretic structures, which clinically manifests as anovulation (Attia *et al*., 2023; Martazanova *et al*., 2023).

No less important is the role of adipose tissue dysfunction, which is no longer viewed as a passive energy depot but is recognised as an active endocrine organ (Kawai *et al*., 2021). Adipocytes secrete a wide range of biologically active substances – adipokines (Tilg *et al*., 2025). In obesity, a state of adipokine imbalance develops: hyperleptinaemia and hypoadiponectinaemia (Walczak & Sieminska, 2021). Leptin, the satiety hormone, in physiological concentrations stimulates GnRH secretion (Childs *et al*., 2021). On the other hand, excessive levels of leptin resistance, a feature of obesity, reduce GnRH pulsation and directly prevent ovarian granulosa cells from synthesising oestradiol (Barca-Mayo & López, 2023). Adiponectin, which has anti-inflammatory and insulin-sensitising effects, is secreted less in obesity. Its low levels exacerbate insulin resistance at the systemic level and directly in the ovaries (Engin, 2024).

A third fundamental component is oxidative stress and chronic systemic low-grade inflammation (Zhang *et al*., 2024). Excess adipose tissue, especially visceral fat, is a source of pro-inflammatory cytokines such as Tumour Necrosis Factor-alpha (TNF-α) and Interleukin-6 (IL-6) (Khalafi *et al*., 2023). These cytokines not only aggravate insulin resistance but also have a direct damaging effect on all stages of the reproductive process (Vilotić *et al*., 2022). Oxidative stress, characterised by an excess of reactive oxygen species, damages lipids, proteins, and DNA of oocytes, disrupts meiosis, leading to the formation of poor-quality embryos with low implantation potential. At the endometrial level, the pro-inflammatory environment and oxidative stress disrupt the processes of apoptosis and angiogenesis, alter the expression of adhesion molecules, and thereby reduce receptivity, making adequate blastocyst implantation impossible (Hussain *et al*., 2021; Deluao *et al*., 2022).

For a holistic understanding of these interrelated processes, **Figure 1** shows a diagram illustrating the pathogenetic cycle.

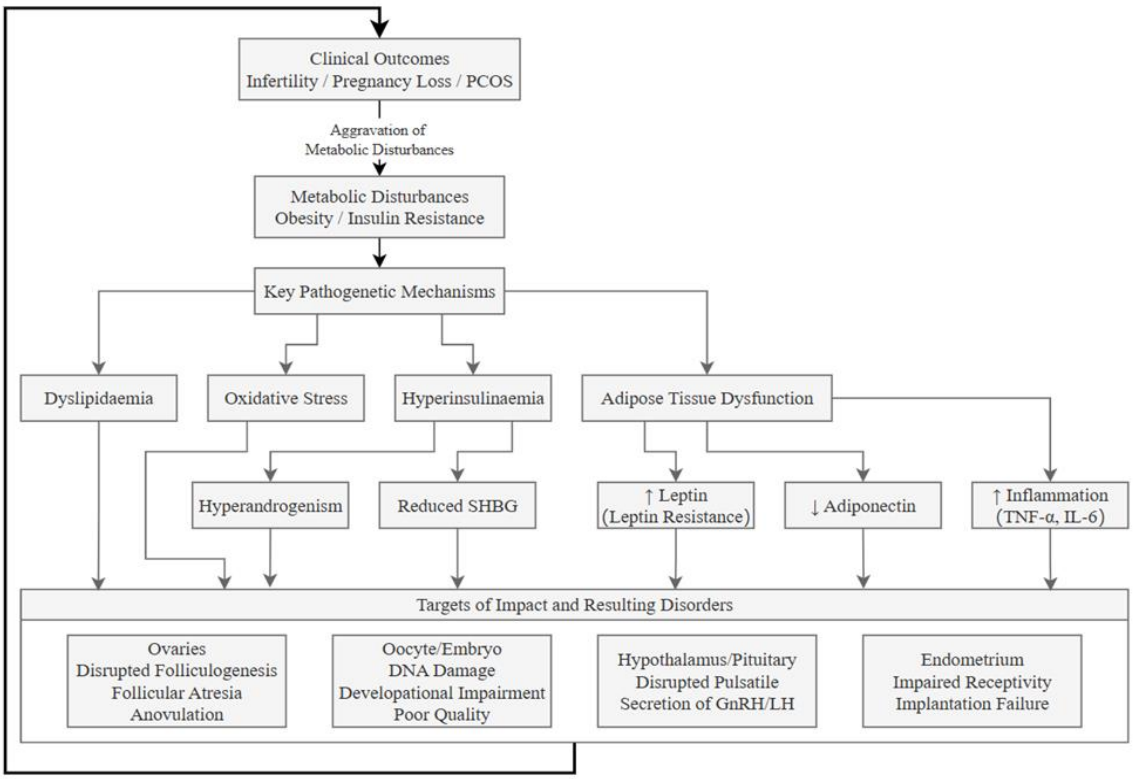

Figure 1. Pathogenetic Pathways Linking Metabolic Disorders with Reproductive Dysfunction

Thus, metabolic disturbances form a self-sustaining vicious cycle, sequentially disrupting the function of all parts of the reproductive system. The aim of this work is a comprehensive analysis of the pathophysiological mechanisms linking metabolic disorders with a wide spectrum of reproductive pathology, and a synthesis of modern data on the diagnosis and correction of these conditions to improve perinatal outcomes. This analysis will require drawing upon an extensive list of literature, encompassing fundamental works on insulin resistance, research in the field of adipokine biology, clinical guidelines for the management of PCOS and infertility, and meta-analyses dedicated to the role of preconception preparation.

Materials and Methods

Study Design and Setting

A prospective cohort study was conducted at the Perinatal Centre of Grozny city (Chechen Republic, Russia) between March 2022 and May 2025. The study protocol was approved by the Local Ethics Committee of the Chechen State University named after A. A. Kadyrov (Grozny, Chechen Republic, Russia) (Protocol No. 145-02/22, dated February 15, 2022), and all participants provided written informed consent before enrolment.

Study Population and Group Allocation

A total of 240 women of reproductive age were recruited and allocated into three study groups. The main group (Group 1, n=120) comprised women diagnosed with either idiopathic infertility or recurrent pregnancy loss, defined as a history of two or more spontaneous miscarriages. The comparison group (Group 2, n=60) consisted of patients with tubal-peritoneal factor infertility, confirmed by laparoscopy or hysterosalpingography, and without clinical or laboratory evidence of metabolic disturbances. The control group (Group 3, n=60) included healthy, fertile parous women with a history of at least one live birth, who presented to the centre for subsequent pregnancy planning.

Inclusion criteria for all participants were age between 25 and 35 years and a regular menstrual cycle lasting 25-35 days. Exclusion criteria comprised a diagnosis of polycystic ovary syndrome, endometriosis (ASRM stage III-IV), type 1 or type 2 diabetes mellitus, decompensated thyroid pathology, and severe extracorporeal pathology of the cardiovascular, respiratory, hepatic, or renal systems.

Clinical, Laboratory, and Instrumental Assessments

All participants underwent a comprehensive examination on cycle days 3-5. Clinical assessment included the collection of general and gynaecological history and anthropometric measurements: height (cm), body weight (kg) for subsequent calculation of body mass index (BMI, kg/m²), and waist and hip circumferences for calculating the waist-to-hip ratio (WHR).

Laboratory diagnostics were performed on venous blood samples collected after a 12-hour overnight fast. Hormonal status was assessed by measuring serum levels of luteinising hormone (LH), follicle-stimulating hormone (FSH), oestradiol, testosterone, prolactin, and thyroid-stimulating hormone (TSH) using an automated immunochemiluminescent analyser. To evaluate insulin

resistance, fasting immunoreactive insulin and plasma glucose levels were measured. The Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) was calculated as [fasting glucose (mmol/L) × fasting insulin (μU/mL)] / 22.5, and the Quantitative Insulin Sensitivity Check Index (QUICKI) was calculated as 1 / [log(fasting insulin, μU/mL) + log(fasting glucose, mg/dL)].

A detailed metabolic profile was further characterised by determining serum concentrations of the adipokines leptin and adiponectin using commercial enzyme-linked immunosorbent assay (ELISA) kits, strictly following the manufacturers' protocols. The state of oxidative stress was assessed by measuring plasma levels of malondialdehyde (MDA) using the spectrophotometric thiobarbituric acid reactive substances (TBARS) method, and by determining the activity of the key antioxidant enzyme superoxide dismutase (SOD) using a commercial reagent kit (Elerian *et al*., 2024; Lee & Ferreira, 2024; Mtenga *et al*., 2024; Rampat *et al*., 2024; Sewankambo, 2024; Xu *et al*., 2024).

Transvaginal ultrasonography was performed using an expert-class ultrasound system with a 7.5 MHz transducer. An ultrasound examination on cycle days 3-5 assessed ovarian reserve by counting the number of antral follicles (2-10 mm in diameter) in both ovaries and measuring ovarian volume using the formula for a prolate ellipsoid (0.523 × length × width × thickness). A follow-up scan during the periovulatory period (days 12-14) evaluated endometrial status by measuring its thickness (M-echo) and visualising its structure, with the presence of a triple-line pattern being noted (Alqahtani *et al*., 2022; Alhussain *et al*., 2022; Brekeit *et al*., 2022; Gu *et al*., 2022; Shcherbin *et al*., 2022; Khazaal *et al*., 2023; Rogers *et al*., 2023; Delcea *et al*., 2024; Yılmazer & Altinok, 2024).

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics software, version 29.0. The normality of the distribution for quantitative variables was tested using the Shapiro-Wilk test. Descriptive statistics for normally distributed continuous variables are presented as mean ± standard deviation (SD), while non-normally distributed data are presented as median and interquartile range (IQR). Categorical variables are described as absolute numbers and percentages (n, %). The three independent groups' continuous variables were compared using one-way analysis of variance (ANOVA) with post-hoc Tukey's test for normally distributed data and the non-parametric Kruskal-Wallis test with pairwise comparisons using Dunn's procedure for non-normally distributed data. Categorical variables were compared using the Chi-square (χ^2) test or Fisher's exact test for expected frequencies less than 5. Correlations between quantitative parameters were assessed using Spearman's rank correlation coefficient (ρ). Statistical significance was set at a two-sided p-value of less than 0.05.

Results and Discussion

The study involved 240 women who were comprehensively examined. The analysis of baseline anthropometric and clinical characteristics revealed significant differences between the groups, as detailed in **Table 2**. Patients in Group 1 (idiopathic infertility/recurrent pregnancy loss) and Group 2 (tubal factor infertility) were comparable in age to the control group ($p>0.05$), confirming the validity of the group matching. However, indicators of metabolic status showed statistically significant deviations. The body mass index (BMI) in Group 1 was significantly higher than in both Group 3 (control) and Group 2 ($p<0.001$). A similar pattern was observed for waist circumference and waist-to-hip ratio, whose values in Group 1 significantly exceeded those in the other two groups ($p<0.01$), indicating a predominance of abdominal obesity. The duration of infertility in the main and comparison groups was comparable, averaging 5.2 and 4.9 years, respectively.

Table 2. Baseline Anthropometric and Clinical Characteristics of the Study Participants (M±SD / Me[Q25; Q75])

Characteristic	Group 1 (n=120)	Group 2 (n=60)	Group 3 (n=60)	p-value
Age, years	30.5 ± 3.8	29.8 ± 4.1	29.1 ± 3.5	0.105
Body Mass Index (BMI), kg/m²	28.9 [26.3; 32.1]	23.4 [21.8; 25.0]	22.1 [20.5; 23.7]	<0.001
Waist Circumference, cm	88.5 ± 9.1	76.2 ± 6.5	72.8 ± 5.9	<0.001
Waist-to-Hip Ratio	0.83 ± 0.06	0.76 ± 0.05	0.74 ± 0.04	<0.01
Infertility Duration, years	5.2 [3.0; 7.0]	4.9 [3.5; 6.5]	-	0.745

The results of the hormonal and metabolic profile assessment, presented in **Table 3**, demonstrated profound disturbances in Group 1 (Alhussain *et al*., 2022; Brekeit *et al*., 2022; Gu *et al*., 2022; Kitama *et al*., 2022; Shcherbin *et al*., 2022; Khazaal *et al*., 2023; Rogers *et al*., 2023; Delcea *et al*., 2024; Yılmazer & Altinok, 2024). While levels of FSH and TSH were comparable across all groups, patients with idiopathic infertility and pregnancy loss had a significantly higher LH/FSH ratio compared to the control and tubal factor groups ($p<0.001$). Furthermore, serum testosterone concentration in Group 1 was more than double that in Group 3 ($p<0.001$). The metabolic parameters were notably altered: fasting insulin and the HOMA-IR index in Group 1 were significantly elevated compared to both Group 2 and Group 3 ($p<0.001$), clearly indicating a state of insulin resistance. Accordingly, the QUICKI index, which reflects insulin sensitivity, was significantly lower in Group 1.

Table 3. Hormonal and Metabolic Profiles of the Study Participants (Me[Q25; Q75])

Parameter	Group 1 (n=120)	Group 2 (n=60)	Group 3 (n=60)	p-value
FSH, IU/L	6.9 [5.8; 8.1]	7.1 [6.0; 8.3]	6.8 [5.9; 7.9]	0.812

LH, IU/L	8.5 [6.4; 11.2]	6.3 [5.2; 7.5]	5.9 [4.8; 6.9]	<0.001
LH/FSH Ratio	1.45 [1.15; 1.80]	0.89 [0.75; 1.05]	0.87 [0.71; 1.02]	<0.001
Testosterone, nmol/L	2.8 [2.3; 3.5]	1.5 [1.2; 1.8]	1.3 [1.1; 1.6]	<0.001
Fasting Insulin, µU/mL	15.8 [12.1; 19.5]	7.2 [5.8; 8.9]	6.5 [5.2; 7.8]	<0.001
HOMA-IR	3.8 [2.9; 4.7]	1.6 [1.3; 2.0]	1.4 [1.1; 1.7]	<0.001
QUICKI	0.325 ± 0.021	0.365 ± 0.018	0.372 ± 0.017	<0.001

The analysis of adipokine status and markers of oxidative stress, summarized in **Table 4**, revealed further significant metabolic disparities. The leptin level in Group 1 was significantly elevated compared to the other groups ($p<0.001$), whereas the concentration of its counter-regulatory hormone, adiponectin, was markedly reduced ($p<0.001$). This resulted in a leptin/adiponectin ratio in Group 1 that was more than four times higher than in the control group ($p<0.001$). The state of oxidative stress was more pronounced in the main group: the concentration of malondialdehyde (MDA) was significantly higher, and the activity of the antioxidant enzyme superoxide dismutase (SOD) was significantly lower compared to Groups 2 and 3 ($p<0.001$).

Table 4. Adipokine Profile and Oxidative Stress Markers (M±SD / Me[Q25;Q75])

Parameter	Group 1 (n=120)	Group 2 (n=60)	Group 3 (n=60)	p-value
Leptin, ng/mL	35.8 [28.4; 44.1]	18.2 [14.5; 22.0]	15.1 [12.0; 18.5]	<0.001
Adiponectin, µg/mL	7.2 ± 1.9	12.5 ± 2.4	13.8 ± 2.1	<0.001
Leptin/Adiponectin Ratio	4.95 [3.80; 6.50]	1.45 [1.10; 1.85]	1.10 [0.85; 1.40]	<0.001
MDA, nmol/mL	6.85 ± 1.12	4.90 ± 0.85	4.55 ± 0.78	<0.001
SOD, U/mL	0.85 [0.72; 0.98]	1.25 [1.10; 1.38]	1.32 [1.18; 1.45]	<0.001

The data from the ultrasound examination of pelvic organs, presented in **Table 5**, indicated significant impairments in the main group (Al-Abbad *et al*., 2022; Ambardekar *et al*., 2022; Atrushi *et al*., 2023; Xie *et al*., 2023; Cissé *et al*., 2024; Ganea *et al*., 2024). The ovarian reserve, assessed by the antral follicle count (AFC), was significantly lower in Group 1 compared to the control group ($p<0.01$). At the same time, the volume of the ovaries in Group 1 was significantly larger than in Groups 2 and 3 ($p<0.05$). In the periovulatory period, the thickness of the endometrium in women with idiopathic infertility and pregnancy loss was significantly less than in the other groups ($p<0.01$), and a morphologically favourable "three-line" endometrium was observed significantly less frequently ($p<0.001$).

Table 5. Ultrasonographic Parameters of Pelvic Organs (M±SD / Me[Q25;Q75] / n(%))

Parameter	Group 1 (n=120)	Group 2 (n=60)	Group 3 (n=60)	p-value
Antral Follicle Count (AFC)	12 [10; 15]	14 [11; 16]	15 [12; 17]	<0.01
Ovarian Volume, cm³	8.5 ± 2.1	7.1 ± 1.6	6.8 ± 1.4	<0.05
Endometrial Thickness, mm (periovulatory)	8.1 ± 1.3	9.8 ± 1.5	10.2 ± 1.4	<0.01
Presence of "Three-Line" Endometrium, n(%)	68 (56.7%)	52 (86.7%)	57 (95.0%)	<0.001

The present study revealed a complex of profound metabolic and endocrine disturbances in patients with idiopathic infertility and pregnancy loss, which reliably distinguish them from both women with tubal factor infertility and healthy fertile women. The obtained data suggest that a significant proportion of cases traditionally classified as "unexplained" infertility have clear pathophysiological mechanisms related to insulin resistance, adipose tissue dysfunction, and oxidative stress.

First and foremost, the pronounced metabolic imbalance in the main group is striking, characterized by a statistically significant increase in body mass index, waist circumference, and waist-to-hip ratio (AlAwwad *et al*., 2022; Dehaghi *et al*., 2022; Huong *et al*., 2022; Singh *et al*., 2022; Bahrawi & Ali, 2023; Jeung & Chang, 2023; Miranda *et al*., 2024; Zhou & Dewey, 2024). These anthropometric parameters unequivocally indicate an abdominal type of obesity, which is a key risk factor for the development of insulin resistance (Neeland *et al*., 2024; Yang *et al*., 2025). This assumption is fully confirmed by the results of laboratory diagnostics: patients in the main group exhibited a significant increase in fasting insulin levels and the HOMA-IR index, alongside a decrease in the QUICKI index. These findings are entirely consistent with the results of numerous studies demonstrating a high prevalence of insulin resistance among women with unexplained infertility and recurrent pregnancy loss (Duffy *et al*., 2021; Guideline Group on Unexplained Infertility *et al*., 2023; Massarotti *et al*., 2024). It is known that hyperinsulinemia, being a compensatory response to decreased sensitivity of peripheral tissues to insulin, has a direct pathological effect on the reproductive system (Chen *et al*., 2022; Yazıcı *et al*., 2024). It potentiates the synthesis of androgens in ovarian theca cells and suppresses the production of sex hormone-binding

globulin in the liver, leading to an increase in the pool of free testosterone (Weger & Gachon, 2021). In our study, this is confirmed by a significant increase in testosterone levels and the LH/FSH ratio in the main group, indicating a disruption in the regulation of the hypothalamic-pituitary-ovarian axis and the development of functional hyperandrogenism (Vale-Fernandes *et al*., 2025).

An important aspect of our study was the comprehensive assessment of adipokine status. We found that women with impaired fertility have a characteristic adipokine imbalance: a significant increase in leptin levels and an equally significant decrease in adiponectin concentration (Zhang *et al*., 2023; Schon *et al*., 2024; Danish *et al*., 2025). Leptin, secreted by adipocytes, under obesity conditions, ceases to be adequately perceived by the hypothalamus, leading to a state of leptin resistance. As shown in experimental and clinical work, high levels of leptin have a suppressive effect on the pulsatile secretion of gonadotropin-releasing hormone, which disrupts the cyclic secretion of LH and FSH and can lead to anovulation (Zhang *et al*., 2023; Schon *et al*., 2024; Danish *et al*., 2025). On the other hand, a deficiency of adiponectin, which has powerful insulin-sensitizing and anti-inflammatory properties, exacerbates insulin resistance and creates a pro-inflammatory background (González-Salazar *et al*., 2025). The most indicative indicator was the calculated leptin/adiponectin ratio, which in the main group was more than four times higher than the control values. In recent years, there has been increasing evidence in the scientific literature that this ratio is a more accurate integral marker of metabolic dysfunction and the associated risk of reproductive impairment than either adipokine separately (Zurita-Cruz *et al*., 2023; Shams *et al*., 2024).

The signs of oxidative stress discovered in our study—increased levels of malondialdehyde and decreased activity of superoxide dismutase—represent another crucial link in the pathogenesis. Oxidative stress is a direct consequence of metabolic disorders, as an excess of free fatty acids in insulin resistance enhances lipid peroxidation (González *et al*., 2023; Masenga *et al*., 2023; Minjares *et al*., 2023). Reactive oxygen species have a damaging effect on all cellular structures. In the context of reproduction, this leads to damage to oocyte DNA, disruption of meiosis processes, and consequently, the formation of low-quality embryos with a high risk of chromosomal abnormalities and subsequent early pregnancy loss. Furthermore, oxidative stress negatively affects the implantation process by disrupting normal endometrial development and receptivity (Cao *et al*., 2022; Smits *et al*., 2023; Begum, 2025). This is confirmed by our ultrasound data, which show that women in the main group had a significantly thinner endometrium in the periovulatory period, and a morphologically complete "three-line" endometrium was observed much less frequently. These findings are consistent with studies showing that hyperglycemia and insulin resistance suppress the expression of key adhesion molecules in the endometrium, such as integrins, thereby disrupting the process of blastocyst apposition and adhesion (Wang *et al*., 2021; Zhu *et al*., 2023).

It is interesting to note that in the comparison group with tubal factor infertility, which was not burdened by metabolic disorders, the indicators of hormonal profile, adipokines, and markers of oxidative stress were almost identical to those in the group of healthy fertile women. This important observation allows us to assert that the identified disturbances are not merely a concomitant background but have a direct pathogenetic connection specifically with fertility impairment of the failed implantation and early pregnancy loss type. The reduced antral follicle count in the main group, coupled with an increase in ovarian volume, may indirectly indicate a disruption in early folliculogenesis and possibly the presence of undiagnosed mild forms of polycystic ovary syndrome that do not fit the strict Rotterdam criteria but significantly affect ovarian reserve and oocyte quality.

Thus, the results of our study collectively paint a holistic picture of metabolically associated reproductive dysfunction. The central link is insulin resistance, which triggers a cascade of interconnected events: hyperinsulinemia and adipokine imbalance lead to hyperandrogenism and dysregulation of the HPO axis, while a pro-inflammatory state and oxidative stress damage oocytes and impair endometrial receptivity. This vicious cycle explains both the difficulties in achieving pregnancy and the high risk of its termination in the early stages (Narula *et al*., 2025). The identified changes necessitate a revision of the diagnostic algorithm for patients with idiopathic infertility and pregnancy loss, mandatorily including not only standard hormonal screening but also an in-depth assessment of metabolic status. The introduction into clinical practice of assessing the HOMA-IR index, the leptin/adiponectin ratio, and markers of oxidative stress will make it possible to identify a subgroup of "metabolic" infertility and prescribe targeted pathogenetic therapy for such patients, aimed at correcting insulin resistance and reducing oxidative stress, which, in turn, could significantly increase the chances of successful conception and pregnancy maintenance.

Conclusion

In conclusion, this prospective cohort study provides compelling evidence that idiopathic infertility and recurrent pregnancy loss are strongly associated with a distinct metabolic phenotype characterized by insulin resistance, adipokine dysregulation, and oxidative stress. The data clearly demonstrate that women in Group 1 exhibited significantly higher metabolic burden compared to both tubal factor infertility and fertile control groups.

The key findings underpinning this conclusion are the profoundly elevated markers of insulin resistance, with a HOMA-IR index of 3.8 [2.9; 4.7] in the main group versus 1.4 [1.1; 1.7] in controls ($p<0.001$), and the severe adipokine imbalance evidenced by a leptin/adiponectin ratio more than four times higher (4.95 [3.80; 6.50]) than in healthy women ($p<0.001$). These metabolic disturbances were further exacerbated by significant oxidative stress, demonstrated by increased MDA levels (6.85 ± 1.12 nmol/mL) and decreased SOD activity (0.85 [0.72; 0.98] U/mL).

These pathological processes manifest clinically through impaired reproductive parameters - notably reduced endometrial thickness (8.1 ± 1.3 mm versus 10.2 ± 1.4 mm in controls) and significantly lower incidence of three-line endometrium pattern (56.7% versus 95.0% in Group 3). The simultaneous presence of these metabolic

and reproductive abnormalities suggests a causal relationship rather than mere association.

Our findings strongly support the concept of "metabolic infertility" as a distinct clinical entity that requires specific diagnostic and therapeutic approaches. The integration of metabolic screening - including HOMA-IR, leptin/adiponectin ratio, and oxidative stress markers - into routine infertility workup could enable earlier identification and targeted intervention for this patient population. Future research should focus on developing standardized diagnostic criteria for metabolic infertility and evaluating the efficacy of metabolic-focused treatments in improving reproductive outcomes in this challenging patient group.

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Ethics statement: The study protocol was approved by the Local Ethics Committee of the Chechen State University named after A. A. Kadyrov (Grozny, Chechen Republic, Russia) (Protocol No. 145-02/22, dated February 15, 2022), and all participants provided written informed consent before enrolment.

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