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Serum Adipokines as Predictive Biomarkers of Endometrial Receptivity in Women with Unexplained Infertility: A Cross-Sectional Study

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ABSTRACT

Background: Even when fertility tests are normal, there can be undetectable metabolic, vascular, and inflammatory changes that affect the receptivity of the endometrium.

Objective: To determine the association of serum leptin, adiponectin, resistin, and the leptin-to-adiponectin ratio with ultrasonographic indicators of endometrial receptivity in women with unexplained infertility.

Methods: This cross-sectional analytical study included 80 women with unexplained infertility at Ghurki Trust Teaching Hospital, Lahore, from January to December 2025. During the mid-luteal implantation window, serum leptin, adiponectin, and resistin were determined by enzyme-linked immunosorbent assays. Transvaginal ultrasound and Doppler were used to measure endometrial thickness, endometrial volume, subendometrial vascularity, and PI of the uterine artery. Logistic regression and receiver operating characteristic analyses were carried out.

Results: A total of 80 women had a receptive and non-receptive endometrial phenotype in 49 (61.3%) and 31 (38.8%) patients, respectively. The non-receptive group had higher leptin, resistin, leptin/adiponectin ratio, body mass index, and insulin resistance but lower adiponectin (all $p<0.05$). Leptin, adiponectin, resistin, and the leptin-to-adiponectin ratio were each independently associated with non-receptivity after adjusting for age, BMI, duration of infertility, and insulin resistance. The leptin/adiponectin ratio was the best individual discriminatory test with an AUC of 0.86, a sensitivity of 80.6%, and a specificity of 79.6%.

Conclusions: There was a strong association between an adverse serum adipokine profile and impaired ultrasonographic endometrial receptivity. The leptin to adiponectin ratio can be viewed as an easy-to-use non-invasive biomarker, but further prospective validation with implantation and live-birth outcomes is needed before its routine clinical use in the assessment, counselling, and treatment planning of infertile patients.

Keywords: adiponectin; endometrial receptivity; leptin; resistin; unexplained infertility

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INTRODUCTION

Unexplained infertility is diagnosed when routine evaluation confirms ovulation, tubal patency, a normal uterine cavity, and semen parameters within accepted limits, yet conception does not occur [1]. There may be an abnormality in embryo development, endometrial function, immune regulation, angiogenesis, or metabolic signalling, which may affect the chance of successful implantation, although there is no apparent abnormality. Impaired endometrial receptivity has come to the fore as one of these mechanisms [2,3].

Endometrial receptivity is a transient state of endometrial function in which it is capable of supporting embryo attachment and invasion and early placental

development [4]. This process takes place within the window of implantation and is reliant on the coordinated hormonal, vascular, inflammatory, and molecular changes [5]. This can occur if the endometrium does not develop properly, or if there is something wrong with the embryo–endometrial communication, although ovulation and fertilization are normal. Ultrasound measurements like endometrial thickness, endometrial volume, subendometrial vascularity, and uterine artery blood flow are commonly used in clinical assessment. But such measurements may not be comprehensive of the biological state of the endometrium [6].

Adipokines are the biologically active mediators mainly secreted by adipose tissue and are now known to play an important role in regulating reproductive function. Leptin, adiponectin, and resistin affect energy metabolism, insulin sensitivity, inflammation, angiogenesis, ovarian function, and embryo implantation. These mediators are also found in reproductive tissues such as endometrium and placenta, indicating that they may have a direct role in implantation and early pregnancy development [7,8].

Leptin is involved in reproductive maturation, vascular development, and trophoblastic activity. But, high circulating levels of leptin could also contribute to inflammatory signalling, oxidative stress, endothelial dysfunction, and leptin resistance, which could negatively influence the endometrial microenvironment [9]. Adiponectin has anti-inflammatory, vascular-protective, and insulin-sensitizing properties. Impaired endometrial perfusion and/or altered glucose metabolism and defective preparation of the endometrium for implantation could then be linked to reduced adiponectin concentrations. Resistin is associated with insulin resistance and activation of inflammation and has been implicated in abnormal endometrial remodelling and vascular dysfunction [10].

It might be more informative to consider the balance between leptin and adiponectin than either of the biomarkers individually. The leptin/adiponectin ratio (L/A) is considered a marker of the balance between pro-inflammatory and insulin-sensitizing adipokine activity. A high ratio can also help to detect women with subclinical metabolic disturbances who might otherwise have normal fertility studies [11].

Although of biological relevance, the role of adipokines in the endometrial receptivity of women with unexplained infertility is poorly characterized [12]. Previous studies have primarily examined outcomes in women with obesity, polycystic ovary syndrome (PCOS), or assisted reproductive outcomes, and there is little evidence on outcomes in women without an identifiable cause of infertility. A non-invasive serum biomarker that reflects the function of the endometrium would be useful to help determine clinically whether a woman's endometrium is functioning normally or if further investigation of her reproductive status would be beneficial [13].

Therefore, this study aimed to evaluate serum leptin, adiponectin, resistin, and the leptin-to-adiponectin ratio in women with unexplained infertility and to determine their associations with ultrasonographic indicators of endometrial receptivity. It also evaluated the possibility of using these adipokines to distinguish receptive and non-receptive endometrial phenotypes [14].

MATERIALS AND METHODS

The study was a cross-sectional analytical study, carried out at the Department of Medicine, Ghurki Trust Teaching Hospital, Lahore, Pakistan, in association with the Departments of Obstetrics and Gynaecology, Radiology, and Pathology from January to December 2025. The study was approved by the Ghurki Trust Teaching Hospital, Lahore (Ref. No. 2025/01/R-03). The study was performed under the principles of the Declaration of Helsinki. All participants gave written informed consent before enrolment, and the confidentiality of the personal and clinical data was respected throughout the study.

The target population consisted of women with unexplained infertility, with a sample size of 80 women who were sampled by using a non-probability consecutive sampling technique. This sample size was determined at 95% confidence level and 80% statistical power for a moderately expected association between serum adipokine concentrations and ultrasonographic indicators of endometrial receptivity. Eligible women were recruited until the desired sample size was achieved and were seen during the study period.

Women of reproductive age (20–38 years) whose pregnancies were not occurring despite at least 12 months of regular unprotected sexual intercourse were included. The diagnosis of unexplained infertility was made after a basic assessment of fertility, which included normal menstrual cycles, patent fallopian tubes on both sides, a normal uterine cavity, and semen analysis of the male partner with values in the accepted laboratory range. Ovulation was confirmed by medical history of menstruation, serial follicular ultrasound, urinary luteinizing hormone (LH) surge, or serum mid-luteal progesterone measurement.

Women with polycystic ovary syndrome, endometriosis, diminished ovarian reserve, hyperprolactinaemia, thyroid dysfunction, congenital uterine abnormalities, intrauterine adhesions, endometrial polyps, submucosal fibroids, hydrosalpinx, and a history of pelvic malignancy were excluded. Subjects with diabetes mellitus, chronic kidney disease, chronic liver disease, autoimmune diseases, acute or chronic infections, and any other systemic diseases that could affect the serum levels of adipokines were also excluded. Women who were taking hormonal therapy or ovulation-induction therapy, insulin-sensitizing, or anti-inflammatory drugs in the previous three months of treatment.

Data was collected on a structured questionnaire for demographic, clinical, and reproductive information. These variables were recorded: age, weight, height, body mass index, type of infertility, the duration of infertility, the length of the menstrual cycle, any prenatal history, previous pregnancy, and previous fertility treatments. Weight was measured on a calibrated digital weighing scale (0.1 kg), and height was measured on a wall-mounted stadiometer (0.1 cm). BMI was defined as the ratio of weight (kg) to height (m)2.

All subjects were tested in a normal menstrual cycle. A single day of ovulation was determined by serial examination of follicles by ultrasound or by detection of the surge of urinary LH. Blood samples and ultrasonographic examination were taken in the mid-luteal phase of the estrous cycle, 6-8 days following the documented ovulation, when the embryos are expected to be in the implantation stage of development.

Following an 8-10-hour overnight fast, about 5 mL venous blood was withdrawn under sterile conditions. Then, the blood has been allowed to coagulate at room temperature and then centrifuged at 3000 RPM for 10 minutes. Separated serum was placed in labelled tubes and frozen at −80°C for biochemical analysis.

The levels of serum leptin, adiponectin, and resistin were determined by commercially available enzyme-linked immunohistochemistry assays (ELISA) based on the manufacturer's guidelines. All serum samples were analysed in duplicate, and laboratory personnel were masked from ultrasonographic results. The serum leptin and resistin concentrations were expressed in nanograms per millilitre, and the serum adiponectin concentration in micrograms per millilitre. The leptin/Adiponectin ratio was obtained by dividing the serum leptin concentration by the serum adiponectin concentration for each individual.

Plasma glucose at fasting was measured by the enzymatic colourimetric method, and the serum glucose, mid-luteal serum progesterone, and fasting serum insulin were measured by the standard immunoassay technique. The homeostatic model assessment of insulin resistance was used for the estimation of insulin resistance. It was derived by taking the product of fasting insulin (μIU/mL) and fasting glucose (mg/dl) and dividing by 405. Supportive evidence of ovulation was provided by mid-luteal serum progesterone.

On the day of blood collection, a transvaginal ultrasonography was performed by an experienced radiologist, who was blinded to the serum adipokine results. Patients were assessed in the lithotomy position with a high-frequency transvaginal probe. The endometrial thickness was measured in the midsagittal plane at the thickest point of the endometrium and was recorded as the thickest double layer (in mm).

Three-dimensional ultrasound was used to determine the volume of the endometrium in cubic centimetres. Subendometrial vascularity was assessed by colour and power Doppler imaging. Colour Doppler signals in the subendometrial area around the endometrial–myometrial junction were taken as evidence of subendometrial blood flow. Bilateral uterine artery waveforms were obtained at the level of the internal cervical os, and the mean uterine artery pulsatility index was calculated from the right and left uterine artery measurements.

A receptive endometrial phenotype was considered to be present if 3 or more of the following findings were observed: endometrial thickness ≥ 7 mm, endometrial volume ≥ 2 cm^3, detectable subendometrial vascularity, and mean uterine artery pulsatility index < 3.0. Those who did not fulfil at least three of these criteria were deemed to have a non-receptive endometrial phenotype. This classification was taken as a non-invasive ultrasonographic evaluation of the endometrium as defined by the study and was not deemed to be equivalent to histological or molecular determination of endometrial receptivity.

The main objective was to determine the relationship between serum leptin, adiponectin, resistin, and the leptin/adiponectin ratio with non-receptive endometrial phenotype. Secondary outcomes measured included the correlation between serum adipokine levels and endometrial thickness, endometrial volume, subendometrial vascularity, and mean uterine artery pulsatility index. The discriminatory potential of each adipokine for a non-receptive endometrial phenotype was also evaluated.

Data entered and analysed using IBM SPSS Statistics version 26.0. Normality of continuous variables was tested by the Shapiro–Wilk test, and they were reported as mean ± S.D. or median (range) depending on the distribution. The data for categorical variables were reported in terms of frequencies and percentages. Normally distributed continuous variables were compared between women with a receptive and non-receptive endometrial phenotype using the independent-samples t-test, and non-normally distributed continuous variables were compared using the Mann–Whitney U test. Fisher's exact test or chi-square test was used to compare categorical variables.

Pearson or Spearman correlation analysis was used to determine the relationship between serum adipokine concentrations and ultrasonographic parameters. Adipokines independently associated with a non-receptive endometrial phenotype were identified by binary logistic regression analysis, adjusting for age, body mass index, duration of infertility, fasting glucose, and insulin resistance. To avoid multicollinearity problems with leptin and adiponectin, the ratio of leptin to adiponectin was used in a separate multivariable model.

The ability of serum leptin, adiponectin, resistin, and the leptin/adiponectin ratio to distinguish between the groups was evaluated by receiver operating characteristic curve analysis. The areas under the curve (AUC) and 95% confidence intervals were computed, and cut-off values were calculated by the Youden index. Sensitivity and

specificity values were determined for each cut-off chosen. Statistically significant p values were set at < 0.05.

RESULTS

A total of 92 women with infertility were assessed during the study period. Twelve were excluded due to polycystic ovary syndrome, thyroid dysfunction, lack of a complete evaluation of the cause of infertility, or inadequate ultrasonographic examination. Eighty women with unexplained infertility were finally analyzed. According to the ultrasonographic criteria established, 49 (61.3%) women were considered as having a receptive endometrial phenotype and 31 (38.8%) as having a non-receptive endometrial phenotype.

The mean age of the participants was 30.7 ± 4.1 years, and the mean infertility period was 4.2 ± 2.0 years. The number of women with primary infertility was 61 (76.3%), and 19 (23.8%) had secondary infertility. The mean BMI was significantly higher in women with a non-receptive endometrial phenotype compared with women with a receptive phenotype (27.3 ± 3.4 kg/m² versus 25.2 ± 3.1 kg/m²; p=0.006). The number of years the women had been infertile was also higher in the non-receptive group (4.8 ± 2.1 versus 3.8 ± 1.8 years; p=0.027). There were no statistically significant differences between the two groups in terms of age, type of infertility, or length of menstrual cycle. Fasting insulin and the homeostatic model assessment of insulin resistance were significantly higher among women with a non-receptive phenotype, whereas mid-luteal progesterone was significantly lower, as presented in Table 1.

The endometrium was thicker and had more endometrial volume in women with a receptive endometrial phenotype compared with those with a non-receptive phenotype. The mean endometrial thickness of the receptive group was 9.3 ± 1.2 mm, while that of the non-receptive group was 6.8 ± 1.0 mm (P< 0.001). Similarly, there was a significant difference in mean endometrial volume between the receptive group (3.3 ± 0.8 cm³) and the non-receptive group (2.1 ± 0.6 cm³; P<0.001).

Subendometrial vascularity was found in 43 women (87.8%) with the receptive phenotype and 10 women (32.3%) with the non-receptive phenotype (p<0.001). There was no significant difference between the mean uterine artery pulsatility index of the non-receptive and receptive groups (2.17 ± 0.38 versus 2.93 ± 0.46; p>0.05).

The serum leptin and resistin levels were significantly increased in women with a non-receptive phenotype. However, the serum levels of adiponectin were significantly reduced in this group. As seen in Table 2, the mean leptin to adiponectin ratio was 3.54 ± 1.47 in women with non-receptive findings and 1.72 ± 0.78 in women with receptive findings (p<0.001).

The serum leptin was negatively correlated with endometrial thickness (r=−0.48; p<0.001) and endometrial volume (r=−0.41; p<0.001) but positively correlated with mean uterine artery pulsatility index (r=0.44; p<0.001). The serum adiponectin was positively related to endometrial thickness (r=0.52; p<0.001) and endometrial volume (r=0.46; p<0.001), and negatively related to uterine artery pulsatility index (r=−0.47; p<0.001). There was a negative correlation between serum resistin and endometrial thickness (r=−0.35; p=0.002) and a positive correlation between serum resistin and uterine artery pulsatility index (r=0.32; p=0.004). The leptin/adiponectin ratio had the highest correlation with endometrial thickness (r=−0.58; p<0.001) and uterine artery pulsatility index (r=0.53; p<0.001).

Univariate analysis was used to test for associations between a non-receptive endometrial phenotype and the various factors, followed by binary logistic regression to find independent factors. Each 5 ng/mL rise in serum leptin was associated with 1.48-fold greater odds of non-receptivity after age was adjusted for, along with BMI, duration of infertility, and insulin resistance. With every 1 µg/mL rise in serum adiponectin, the risk of non-receptivity decreased by 29%. Non-receptive findings were also independently related to serum resistin.

Due to the mathematical relationship between leptin and adiponectin, the leptin/adiponectin ratio was evaluated in a separate adjusted model. For each one-unit increment in the ratio, the odds of having a non-receptive endometrial phenotype increased by 1.89-fold.

The leptin/adiponectin ratio demonstrated the highest discriminatory power among the individual adipokines, with an area under the curve of 0.86. At a cut-off value greater than 2.30, the ratio identified non-receptive endometrial findings with 80.6% sensitivity and 79.6% specificity. The combined biomarker model of leptin, adiponectin, and resistin showed an area under the curve of 0.90 with 83.9% sensitivity and 83.7% specificity, as shown in Table 3.

The individual adipokine model was controlled for age, body mass index, duration of infertility, insulin resistance, leptin, adiponectin, and resistin. The leptin-to-adiponectin ratio was examined in a separate model adjusted for age, body mass index, duration of infertility, and insulin resistance.

Table 1: Clinical and metabolic characteristics according to endometrial receptivity phenotype

Variable	Receptive phenotype, n=49	Non-receptive phenotype, n=31	p-value
Age, years	30.3 ± 4.0	31.3 ± 4.2	0.291
Body mass index, kg/m²	25.2 ± 3.1	27.3 ± 3.4	0.006
Duration of infertility, years	3.8 ± 1.8	4.8 ± 2.1	0.027
Primary infertility	37 (75.5%)	24 (77.4%)	0.846
Secondary infertility	12 (24.5%)	7 (22.6%)	0.846
Menstrual-cycle length, days	28.6 ± 1.8	29.1 ± 2.0	0.249
Fasting plasma glucose, mg/dL	91.5 ± 8.4	95.7 ± 9.1	0.038
Fasting serum insulin, µIU/mL	9.7 ± 3.3	12.6 ± 4.1	0.001
Homeostatic model assessment of insulin resistance	2.2 ± 0.8	3.0 ± 1.1	<0.001
Mid-luteal progesterone, ng/mL	15.1 ± 4.6	12.8 ± 4.0	0.024

Table 2: Ultrasonographic findings and serum adipokine concentrations

Variable	Receptive phenotype, n=49	Non-receptive phenotype, n=31	p-value
Endometrial thickness, mm	9.3 ± 1.2	6.8 ± 1.0	<0.001
Endometrial volume, cm³	3.3 ± 0.8	2.1 ± 0.6	<0.001
Detectable subendometrial vascularity	43 (87.8%)	10 (32.3%)	<0.001
Mean uterine artery pulsatility index	2.17 ± 0.38	2.93 ± 0.46	<0.001
Serum leptin, ng/mL	17.4 ± 5.8	24.6 ± 7.3	<0.001
Serum adiponectin, µg/mL	11.0 ± 2.9	7.7 ± 2.4	<0.001
Serum resistin, ng/mL	7.0 ± 1.8	9.1 ± 2.2	<0.001
Leptin-to-adiponectin ratio	1.72 ± 0.78	3.54 ± 1.47	<0.001

Table 3: Multivariable associations and discriminatory performance of serum adipokines

Biomarker or model	Adjusted odds ratio for non-receptivity	95% confidence interval	p-value	Area under the curve	Suggested cut-off	Sensitivity	Specificity
Leptin, per 5 ng/mL increase	1.48	1.08–2.04	0.015	0.78	>20.5 ng/mL	74.2%	71.4%
Adiponectin, per 1 µg/mL increase	0.71	0.57–0.88	0.002	0.81	<9.1 µg/mL	77.4%	75.5%
Resistin, per 1 ng/mL increase	1.32	1.04–1.68	0.024	0.74	>8.0 ng/mL	67.7%	69.4%
Leptin-to-adiponectin ratio, per unit increase	1.89	1.27–2.81	0.002	0.86	>2.30	80.6%	79.6%
Combined adipokine model	—	—	<0.001	0.90	Predicted probability	83.9%	83.7%

DISCUSSION

The current study was aimed at determining the correlation between adipokines and ultrasonographic markers of endometrial receptivity in women with unexplained infertility [15,16]. Non-receptive women had significantly higher serum leptin concentration, resistin concentration, lower adiponectin concentration, and leptin/adiponectin ratio, compared with receptive women. These differences were also present after adjustment for age, body mass index, duration of infertility, and insulin resistance, suggesting that altered adipokine activity may be linked to endometrial dysfunction, independent of conventional metabolic parameters [17,18].

In the women with non-receptive endometrial findings, there was a significant increase in serum leptin [19]. It was also negatively associated with endometrial thickness and endometrial volume, and positively associated with uterine artery pulsatility index. Leptin plays an important physiological role in reproductive maturation, angiogenesis, trophoblastic development, and implantation. Too much leptin, however, can be a sign of a problem with adipose tissue, chronic low-level inflammation, and decreased leptin sensitivity. These disturbances can have a negative impact on the cellular signalling, vascular development, and embryo–endometrial communication of the endometrium [7-11].

This association of elevated leptin with increased uterine artery resistance may have clinical implications [1,2]. Endometrial growth, oxygen, nutrients, and preparation for implantation depend on adequate blood flow between the uterus and the subendometrium [3]. An upregulation of leptin-induced inflammatory and endothelial effects could lead to diminished vascular relaxation and the possibility of diminished endometrial perfusion. There was also an observed negative correlation between leptin and endometrial thickness and volume, which also suggests a potential association between overactive leptin and poor endometrial development [4].

An opposite pattern was seen for adiponectin. The serum adiponectin levels were significantly higher in women with a receptive endometrial phenotype [5-7]. There was a positive correlation between adiponectin and endometrial thickness and volume, and a negative correlation between adiponectin and uterine artery pulsatility index. This may be due to the insulin-sensitizing, anti-inflammatory, and vascular-protective properties of adiponectin. Sufficient adiponectin activity could help maintain the function of the endothelium, cellular glucose

utilization, and proper endometrial remodeling during the implantation window [6,11].

Low levels of adiponectin may indicate a poor metabolic and inflammatory profile even in women without apparent POCS or diabetes [5,9]. In the current study, the relationship between adiponectin and endometrial receptivity was also present after controlling for body mass index (BMI) and insulin resistance. This indicates that adiponectin might be an extra parameter in the evaluation of the endometrial function, in addition to the classical anthropometric and metabolic parameters [10,15].

The serum resistin level was also significantly high in women with a non-receptive phenotype. Resistin is linked to inflammatory activation, insulin resistance, endothelial dysfunction, and vascular response changes [1,3,14]. These effects could lead to diminished endometrial blood flow and abnormal tissue remodelling. While resistin showed less discriminatory power than leptin or adiponectin, it was still independently associated with non-receptive findings and might play a role in a more general metabolic inflammatory pattern [19]. Of the individual biomarkers, the leptin/adiponectin ratio was most closely associated with unfavorable endometrial findings [4-6]. The higher the ratio, the more pro-inflammatory the leptin and the less anti-inflammatory the adiponectin. Each one-unit rise in the ratio was significantly correlated with higher odds for a non-receptive endometrial phenotype in this study. The ratio was also found to have better association with uterine artery resistance and endometrial thickness than either of the biomarkers alone [7-10].

The leptin/ adiponectin ratio had good discriminatory ability with an area under the curve equal to 0.86. It had good sensitivity and specificity at the proposed cut-off value to detect women with non-receptive findings. The multi-marker model (combined adipokine model) was even more effective, suggesting that a multi-marker approach might be more useful than the measurement of any adipokine alone [1-5].

Biologically, it is plausible that the combined model outperforms as endometrial receptivity is controlled by several interacting processes such as hormonal responsiveness, vascular development, immunity, inflammation, cellular metabolism, and embryo-derived signalling [6]. As leptin, adiponectin, and resistin may reflect distinct aspects of endometrial dysfunction, a panel of these three markers might identify this dysfunction better than using any single marker alone [17].

The non-receptive phenotype was also associated with an increase in body mass index, fasting insulin, fasting glucose, and insulin resistance in women [18]. These results show that even women without known metabolic disease may be influenced by subtle metabolic abnormalities, which may affect endometrial development. Multivariable adjustment, however, revealed that the body mass index was not enough to account for the difference in adipokines. The results confirm the usefulness of biochemical markers in addition to anthropometric measurements [19].

The results could be clinically significant for women who experience unexplained infertility, where the standard tests do not reveal a clear cause. Serum adipokine measurement could be a relatively non-invasive way of identifying women who may have some metabolic, vascular, or inflammatory endometrial disturbance. These patients may be candidates for more detailed evaluation of the endometrium or more intensive evaluation of metabolism before fertility treatment [13,20].

However, there are several limitations to consider when interpreting the findings. This is a cross-sectional design, and it cannot be concluded that the decrease in adipokines causes decreased endometrial receptivity [5-7]. Whether the abnormalities in the endometrium were attributed to the adipokine abnormalities or whether the adipokine abnormalities were a consequence of the other metabolic abnormalities could not be determined. In this study, the term predictive is used in the sense of discriminatory power of the statistics, not in the sense of predicting prospective implantation or pregnancy [13-15].

The study measured the endometrial receptivity using a study-defined ultrasonographic and Doppler phenotype and not by histological examination, transcriptomic testing, or actual implantation outcome [16,17]. The parameters chosen give useful practical data on endometrial development and blood flow, and can only be an approximation of the complex molecular state of the implantation window. The study was also carried out at one centre with a rather small sample size, and the suggested cut-off values may not apply to other settings or be stable [18].Factors like diet, exercise, body-fat distribution, sleep patterns, and low-grade inflammation were not thoroughly evaluated. Furthermore, pregnancy, implantation, miscarriage, and live birth outcomes were not assessed. So the clinical value of these biomarkers is still unclear for predicting reproductive success [19].

Larger, more diverse populations should be used in future prospective studies and assays for serum adipokines performed before natural conception or assisted reproductive treatment [4]. Relationships between them and implantation, clinical pregnancy, miscarriage, and live birth should be investigated. Comparisons with markers in endometrial tissue, molecular tests of receptivity, and concentrations of adipokines in endometrial fluid may also help to explain the biological mechanisms [15,19].

CONCLUSION

Women with unexplained infertility and a non-receptive endometrial phenotype had higher serum leptin and resistin concentrations, lower adiponectin concentrations, and an increased leptin-to-adiponectin ratio. These adipokines were significantly correlated with endometrial thickness, endometrial volume, subendometrial vascularity, and uterine artery resistance. The leptin/adiponectin ratio

showed the best individual biomarker discriminatory ability, and the correlation of adipokines model showed the best overall discriminatory ability. These results indicate that serum adipokines might be a convenient and non-invasive marker for endometrial dysfunction in women with unexplained infertility. But further validation in using them as predictors of implantation, pregnancy, and live birth outcomes is needed before recommending their routine clinical use.

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Authors' Contributions: H.K. conceived the study and drafted the manuscript. A.S. supervised and revised the work. M.T. analyzed the data and edited the manuscript. All authors approved the final version.

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Data Availability: Data are available from the corresponding author upon reasonable request.

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