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The effect of low-dose naltrexone on immunological infertility in women with recurrent implantation failure

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Recurrent implantation failure (RIF) is a considerable problem in assisted reproductive technologies, especially in the cases which are associated with immunological infertility. Low-dose naltrexone (LDN) has surfaced as a prospective treatment for several illnesses owing to its immunomodulatory characteristics.
The objective: **to study the impact of LDN on the pregnancy course in women with immunological infertility and RIF.**
Materials and methods**. A total of 350 women aged 18–40 years with RIF and immunological infertility, who were examined and treated in the United Surgeons Fertility Center in Baghdad between January 1, 2024, and January 1, 2025, participated in the study. Participants were further divided into two groups. The treatment group included 175 women who received LDN 4.5 mg orally daily before pregnancy and during the first 12 weeks of pregnancy. The control group consisted of 175 women who did not receive naltrexone. The study examined clinical parameters such as endometrial thickness, ovarian follicular response, immune markers, and pelvic ultrasound findings.**
Results**. The group of women who received low doses of naltrexone had an increased endometrial thickness of 9.8 mm (26.9 mm vs 21.1 mm) compared to the control group. In the treatment group more mature follicles, better ovarian response, and better endometrium were determined. The treatment group also had lower concentrations of immune markers and antinuclear antibody levels than the control group. Pregnancy rates (pregnancy rate, number of successful embryo implantations, duration of pregnancy to 12 weeks) were greater in the treatment group than in the control group.**
Conclusions**. The results of the study indicate the prospect of implementing a new treatment method for women with immunological infertility and RIF. However, additional studies with a larger number of samples are needed to confirm the current efficacy and safety of LDN in the treatment of immunological infertility.**
Keywords**:** *recurrent implantation failure, low-dose naltrexone, fertility, immunological infertility, pregnancy outcomes.*

Вплив низьких доз налтрексону на імунологічне безпліддя у жінок із повторною невдачею імплантації

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Повторна невдача імплантації (ПНІ) є значною проблемою при безплідді, яке лікується за допомогою допоміжних репродуктивних технологій, особливо у випадках імунологічного безпліддя. Налтрексон у низьких дозах (ННД) є засобом для лікування певних захворювань завдяки своїм імуномодулювальним характеристикам.
Мета дослідження: дослідити вплив ННД на перебіг вагітності у жінок з імунологічним безпліддям та ПНІ.
Матеріали та методи. Загалом у дослідженні взяли участь 350 жінок віком 18–40 років з імунологічним безпліддям та ПНІ, які проходили обстеження й лікування в United Surgeons Fertility Center (Багдад, Ірак) у період із 1 січня 2024 по 1 січня 2025 року. Учасниці були розділені на дві групи. До групи лікування увійшло 175 жінок, які отримували ННД по 4,5 мг перорально щоденно до вагітності та протягом перших 12 тиж. вагітності. Контрольну групу становили 175 жінок, які не отримували налтрексон. У дослідженні вивчали такі клінічні параметри: товщина ендометрія, фолікулярна відповідь яєчників, імунні маркери та результати ультразвукового дослідження органів малого таза.
Результати. Порівняно з контрольною групою, у групі жінок, які отримували низькі дози налтрексону, встановлено збільшення товщини ендометрія на 9,8 мм (26,9 проти 21,1 мм). У цій групі також виявлено більш зрілі фолікули, кращу реакцію яєчників і якісніший ендометрій. У групі лікування також встановлено нижчі концентрації імунних маркерів і рівнів антинуклеарних антитіл, ніж у контрольній групі. Показники вагітності (частота настання вагітності, кількість успішних імплантацій ембріона, тривалість вагітності до 12 тиж.) у групі лікування були більшими, ніж у контрольній групі.
Висновки. Результати дослідження вказують на перспективу впровадження нового методу лікування жінок з імунологічним безпліддям і ПНІ. Проте необхідні додаткові дослідження з більшою кількістю зразків, щоб підтвердити поточну ефективність і безпеку ННД в терапії імунологічного безпліддя.
Ключові слова: *повторна невдача імплантації, низька доза налтрексону, фертильність, імунологічне безпліддя, наслідки вагітності.*

Recurrent implantation failure (RIF) is a notable medical challenge in reproductive medicine, particularly, in assisted reproductive technologies like *in vitro* fertilization (IVF). RIF is generally described as the inability to implant an embryo after three or more consecutive failed IVF efforts, notwithstanding the transfer of high-quality embryos. An embryo fails to implant is one of the bitterest, most tragically enjoyable frustrations that patients and doctors encounter daily [1]. About 10–15% of IVF patients will have RIF, resulting in emotional suffering for many wounded individuals and families involved in each case. Also, it can lead to prolonged and expensive therapy. The study of underlying causes of RIF and the development if effective therapy approaches will help patients to achieve better results [2].

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RIF is influenced by many factors, such as the quality of the embryos, uterine receptivity and maternal immunity. Immunological infertility theories play a significant role in explaining how embryo implantation fails in some cases on the first try. Immune-related factors impede the implantation process. An unfavorable environment can be produced in the uterus when natural killer (NK) cell levels increase, cytokine concentrations become imbalanced, and autoimmunity is present in either direction. It is known, that an overreacting immune system will regard the embryo as an invader, and the environment in which it is developed becomes highly inappropriate for successful implantation. Conventional fertility treatments, such as IVF, are likely to fail in immune-mediated RIF. So, alternative therapeutic options are now needed to adjust the immune competency of the receptor [3].

One such promising treatment is the use of low-dose naltrexone (LDN). Naltrexone is an opioid receptor antagonist. It has traditionally been used in heroin addiction and alcohol dependence therapy. However, recent research has shown that low doses of naltrexone have immune-modulating effects that could be beneficial for several health problems, including various autoimmune diseases as well as chronic pain complaints [4]. LDN functions by temporarily obstructing opioid receptors, resulting in a compensatory elevation in the synthesis of endogenous opioids, including endorphins. Endogenous opioids are thought to possess immunoregulatory effects, including modulation of inflammation and inhibition of excessive immunological responses. Hence, LDN has recently attracted attention as an approach to treat such conditions involving altered immune function as infertility potentially [5].

In terms of fertility, LDN has been used as a potential treatment means for women suffering from hypothalamic ovarian dysfunction. In some cases, it has already been used to stimulate ovulation that has not been achieved with any other method of treatment [6]. However, its application in women with autoimmune problems, particularly those suffering from recurrent pregnancy loss or embryo implantation failure, has not been extensively explored. Immune response modulation, in particular NK cell activity suppression and autoimmunity-factor coordination, is vital for improving endometrial receptivity and aiding implantation success. This aspect of immunological infertility makes LDN interesting for patients with RIF of an immune nature [7]. For women with immune-based RIF, LDN is an exciting candidate as a means of improving outcomes. However, literature about the impact of LDN on fertility for women who have immune-system infertility remains is not enough evidence. Naltrexone is most frequently used in treating chronic pain and autoimmune diseases [8].

Understanding the endometrium

Endometrium is the mucous membrane that borders the inside of the uterus in females. The thickness of the endometrium continues to augment during the menstrual cycle (Fig. 1). If embryo implantation does not take place, it is expelled as menstrual flow. In summary, endometrial thickness fluctuates according to the several phases of the menstrual cycle [9]. Upon the encounter of sperm and egg, leading in fertilization within the fallopian tube, the ensuing embryo commences its transit to the uterus to implant in the uterine lining. Embryo implantation needs an endometrial thickness of around 7 to 10 mm. This often occurs spontaneously between the 19th and 21st days of the cycle, which is regarded as the receptive period of the endometrium or implantation window [10].

The endometrium is responsive when it attains appropriate thickness throughout the menstrual cycles secretory phase. Furthermore, an ultrasound scan would reveal a triple line appearance. The ovarian female sex hormones are responsible for enhancing endometrial thickness and inducing a triple line look. Every one of these attributes are essential for embryo implantation (Fig. 2) [12].

Moreover, the synchronicity between embryo and endometrial growth is an additional feature that enhances the likelihood of implantation. This synchronicity arises from the influence of cytokines and multiple growth variables that promote the fertilization of embryos [14].

Implantation in the endometrium

The embryo implants in the endometrium around 6 to 7 days post-fertilization, during the blastocyst stage. For this, there must be impeccable synchrony between the developing child and the endometrium, specifically, there must be menstrual receptivity [13]. Several investigations involving patients have determined that the ideal endometrial thickness for successful implantation ranges from 7 to 10 mm [15, 16]. An endometrium measuring less than 6 mm often inhibits embryo implantation (Fig. 3) [17].

Not only the endometrium must be sufficiently hormonal prepared for effective implantation, but the blastocyst tissues and the uterine mucosa must also engage in a reciprocal conversation. Different growth factors and cytokines must function in this regard [18]. Upon successful fertilization

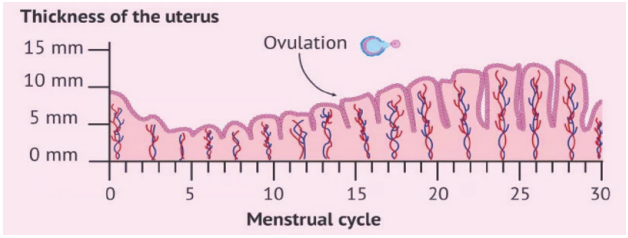

Fig. 1. The relation between endometrial thickness and menstrual cycle [11]

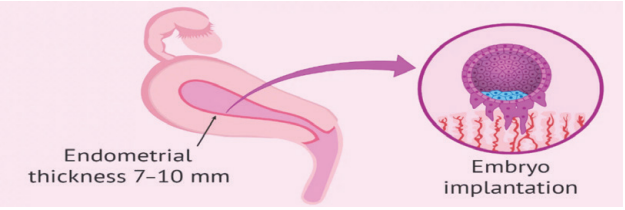

Fig. 2. Endometrial receptivity pattern [13]

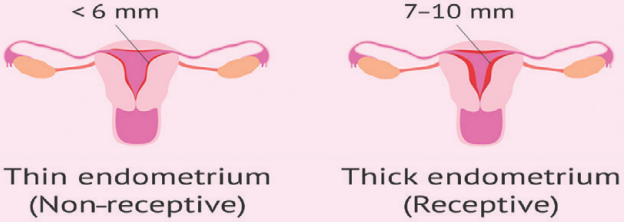

Fig. 3. Endometrial implantation window [17]

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of the ovum and subsequent implantation of the embryo, the secretory endometrium undergoes specialization due to the influence of estrogens and progesterone, a process referred to as decidualization. The decidual or decidualized endometrium is a specialized structure that develops into the placenta during gestation and facilitates the flow of gasses and minerals between the mother and the embryo [19].

The objective is to study the effects of LDN on human reproduction by evaluating its use in women with immunological infertility and RIF.

MATERIALS AND METHODS

Study design. The study was carried out from January 1, 2024, to January 1, 2025, at United Surgeons Fertility Center. A total of 350 women aged 18–40 years participated in the study. All of them had experienced RIF (defined as the failure to achieve clinical pregnancy after three or more embryo transfers). The patients were divided into two groups – 175 women assigned to the treatment group (LDN treatment group) and 175 women – control group.

Participant recruitment. When the patients entered the research program, each underwent an initial screening. Then the data were examined in detail. The diagnostic workup included taking complete medical histories, gynecological examinations, comprehensive infertility assessments, hormonal level determination, pelvic ultrasound imaging, and evaluation of immune markers. The prospective patients who had immunity infertility factors such as elevated levels of NK cells and abnormal autoantibody concentrations were also enrolled.

Women in the treatment group received LDN 4.5 mg of LDN orally every day for 10 weeks before conception, and therapy was continued until the pregnancy was confirmed at 12 weeks gestation. The control group received no intervention.

Throughout the duration of the study, researchers conducted a monthly visit. These affairs involved measurements as varied and sensitive as hormone profiles (e.g., follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol and progesterone), immune markers and ultrasound findings. Hormonal levels and immune markers were measured on the 3rd day of the menstrual cycle for all participants, unless otherwise specified by using, enzyme-linked immunosorbent assay (ELISA). The FSH, LH, estradiol, progesterone, NK cells, antinuclear antibodies (ANA), antiphospholipid antibodies (APA) serum kits used in this study was purchased from Sunlong Biotech (China). Resulting the embryo transfer outcomes followed a process in which pregnancy rates, implantation rates (addressing that question on how to improve the number of embryo implants) were all measured and recorded. Clinical pregnancy rates were also documented.

The ultrasound imaging was performed using a Voluson E10 Ultrasound Machine (GE Healthcare). Ultrasound imaging was conducted at baseline, as well as at various stages during the IVF process, including monitoring of endometrial thickness, ovarian response, and the presence of any abnormalities. Results were compared between the treatment group and the control group.

Statically analysis. Data analyzed by using SPSS Version 22. Descriptive statistics (mean, standard deviation, percentages) will summarize clinical characteristics and immune markers. To compare baseline characteristics between groups, independent t-tests used to depend on data distribution. Pregnancy rates, implantation rates, and clinical pregnancy compared between groups using chi-square or Fisher's exact tests. Changes in immune markers and hormone levels compared using paired t-tests. Multivariate regression analysis may be used to adjust for confounders. A p-value of < 0.05 will be considered statistically significant.

Ethical considerations. In this study, ethical guidelines from the institution's review board were followed and aspects of the Declaration of Helsinki were adhered to. Prior to undergoing randomization all participants had given written informed consent. They were given a clear picture of the study's purpose, how it would proceed, any possible risks involved, and benefits to be had. Participants were free to quit at any point in time, they had that right. The whole research process was conducted behind the scenes, the data source was stripped of any possibility or identification. Ethical approval for the study was provided by the appropriate Ethics Committee.

RESULTS AND DISCUSSION

The average age of participants was 32.5 ± 4.6 years, with no significant difference between the two groups. Prior to the intervention, women in the both groups had a history of multiple failed embryo transfers (at least three failed embryo transfers) and were diagnosed with immunological infertility, based on elevated NK cells or other immunological markers. The baseline characteristics of the treatment group LDN and the control group were compared to ensure comparability between the two groups before the intervention. As shown in the Table 1 these results indicated that the two groups were well-matched in terms of baseline demographics and clinical characteristics.

In Table 2 comparison of hormone levels before and after treatment in both the treatment group (LDN) and the control group is presented. Indicating that LDN treatment had a significant effect on increasing progesterone levels compared to the control group.

The comparison of immune markers before and after treatment between the treatment group (LDN) and the control group demonstrated that NK cells were decreased significantly in the treatment group, from 18.3 ± 3.1% to 12.5 ± 2.4%, while the control group remained stable, with a slight change from 18.1 ± 2.9% to 17.9 ± 3.2% (Table 3). This difference was statistically significant ($p = 0.02$), indicating that LDN treatment had a notable effect in reducing NK cell levels. Regarding ANA, the treatment group experienced a significant reduction from 4.5 ± 1.2 mIU/mL to 3.1 ± 1.0 mIU/mL, while the control group showed a minor decrease from 4.3 ± 1.3 mIU/m to 4.2 ± 1.4 mIU/mL. The difference between the groups was statistically significant ($p = 0.04$), suggesting that LDN treatment also contributed to a reduction in ANA levels. For APA, both groups exhibited slight decreases, with the treatment group showing a reduction from 2.6 ± 0.9 mIU/mL to 1.9 ± 0.7 mIU/mL, and the control group changing from 2.5 ± 1.0 mIU/mL to 2.4 ± 0.8 mIU/mL. However, this change was not statistically significant ($p = 0.18$), indicating that LDN did not significantly impact APA levels compared to the control group (Table 3).

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Endometrial thickness showed a significant improvement in the treatment group, increasing from 7.2 ± 1.0 mm to 9.8 ± 1.2 mm, while the control group showed a modest increase from 7.4 ± 1.1 mm to 7.6 ± 1.0 mm (Table 4; Fig. 4). The difference between the two groups was statistically significant (p = 0.001), indicating that LDN treatment had a substantial effect on increasing endometrial thickness. For ovarian response, the treatment group showed a significant increase in the number of follicles ≥ 18 mm, rising from 3.4 ± 1.2 to 5.1 ± 1.5, while the control group showed a smaller increase from 3.3 ± 1.1 to 3.4 ± 1.2 (Fig. 5). This difference was statistically significant (p = 0.02), suggesting that LDN treatment improved ovarian response.

Lastly, endometrial pattern also showed improvement in the treatment group, with a significant increase in grade from 2.8 ± 0.4 to 3.7 ± 0.5. The control group showed a smaller increase from 2.9 ± 0.5 to 3.0 ± 0.4, and the difference between the groups was statistically significant (p = 0.03) (Fig. 6), indicating that LDN treatment contributed to a more favorable endometrial pattern. Overall, the results suggest that LDN treatment had a positive impact on endometrial thickness, ovarian response, and endometrial pattern, all of which are crucial factors for successful implantation and pregnancy outcomes (Table 4).

The pregnancy rate in the treatment group was significantly higher compared to the control group. Similarly, the implantation rate was significantly higher, suggesting that LDN treatment enhanced embryo implantation success. The clinical pregnancy rate was also higher in the treatment group compared to the control group, indicating that LDN had a significant positive effect on the clinical pregnancy rate. However, the miscarriage rate was lower in the treatment group (8%) compared to the control group (12%), but this difference was not statistically significant (p = 0.15), suggesting that LDN did not have a significant impact on reducing miscarriage rates (Table 5). Overall, LDN treatment was associated with significantly higher pregnancy, implantation, and clinical pregnancy rates compared to the control group, highlighting its potential effectiveness in improving fertility outcomes in women with RIF.

A strong positive correlation indicates that the treatment improves the uterine lining, creating more favorable conditions for pregnancy. LDN has a strong positive impact on ovarian response, as reflected by an increased number of mature follicles. This suggests that LDN enhances ovarian function, possibly improving oocyte quality, crucial for fertilization and embryo development. LDN can improve the quality of the endometrial pattern as well as enhance uterine receptivity to embryo implantation. This strong positive correlation demonstrates that LDN contributes to a better-quality uterine lining. LDN has

Table 1

Group Demographics and Baseline Parameters

Parameters	Treatment Group (LDN) (n = 175)	Control Group (n = 175)	p-value
Age (mean ± SD), years	32.5 ± 4.6	32.7 ± 4.5	0.75
BMI (mean ± SD), kg/m²	25.6 ± 3.2	25.3 ± 3.1	0.61
Number of failed IVF cycles	4.2 ± 1.3	4.1 ± 1.2	0.88
Hypertension	9 (5.1%)	11 (6.3%)	0.67
Diabetes mellitus	6 (3.4%)	7 (4.1%)	0.79

Notes: BMI – body mass index; IVF – *in vitro* fertilization.

Table 2

Hormonal Levels at Baseline and Post-Treatment

Hormones	Treatment Group (LDN) Pre-Treatment (n = 175)	Treatment Group (LDN) Post-Treatment (n = 175)	Control Group Pre-Treatment (n = 175)	Control Group Post-Treatment (n = 175)	p-value Post-Treatment between groups
FSH (mIU/mL)	6.2 ± 1.1	5.9 ± 1.0	6.1 ± 1.2	6.3 ± 1.3	0.54
LH (mIU/mL)	5.6 ± 1.3	5.2 ± 1.2	5.4 ± 1.1	5.5 ± 1.2	0.61
Estradiol (pg/mL)	98.2 ± 15.3	103.6 ± 17.5	95.6 ± 16.4	96.4 ± 17.8	0.32
Progesterone (ng/mL)	1.2 ± 0.4	2.8 ± 1.1	1.3 ± 0.5	1.5 ± 0.6	0.01

Notes: FSH – follicle-stimulating hormone; LH – luteinizing hormone.

Table 3

Immunological Parameters

Parameters	Treatment Group (LDN) Pre-Treatment (n = 175)	Treatment Group (LDN) Post-Treatment (n = 175)	Control Group Pre-Treatment (n = 175)	Control Group Post-Treatment (n = 175)	p-value Post-Treatment between groups
NK cells (%)	18.3 ± 3.1	12.5 ± 2.4	18.1 ± 2.9	17.9 ± 3.2	0.02
ANA (mIU/mL)	4.5 ± 1.2	3.1 ± 1.0	4.3 ± 1.3	4.2 ± 1.4	0.04
APA (mIU/mL)	2.6 ± 0.9	1.9 ± 0.7	2.5 ± 1.0	2.4 ± 0.8	0.18

Notes: NK – natural killer; ANA – antinuclear antibodies; APA – antiphospholipid antibodies.

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Table 4

Ultrasound and Sonographic Findings

Parameters	Treatment Group (LDN) Pre-Treatment (n = 175)	Treatment Group (LDN) Post-Treatment (n = 175)	Control Group Pre-Treatment (n = 175)	Control Group Post-Treatment (n = 175)	p-value Post-Treatment between groups
Endometrial thickness (mm)	7.2 ± 1.0	9.8 ± 1.2	7.4 ± 1.1	7.6 ± 1.0	0.001
Ovarian response (follicles ≥ 18 mm)	3.4 ± 1.2	5.1 ± 1.5	3.3 ± 1.1	3.4 ± 1.2	0.02
Endometrial pattern (grade)	2.8 ± 0.4	3.7 ± 0.5	2.9 ± 0.5	3.0 ± 0.4	0.03

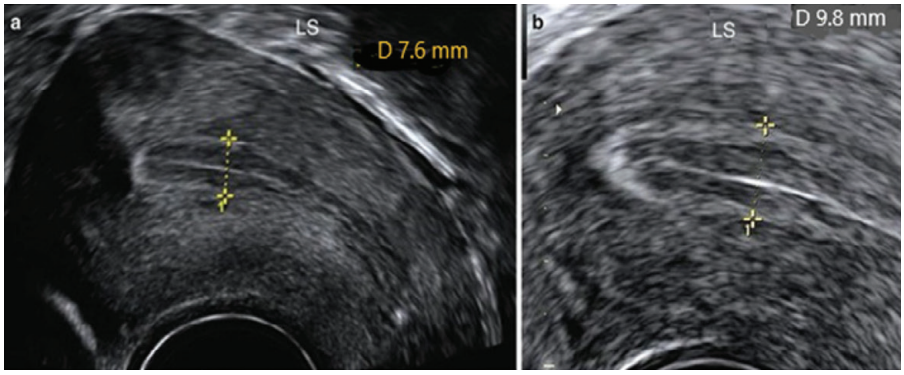

Fig. 4. Ultrasound of Endometrial thickness (a woman 20 years old; the 5th day of the menstrual cycle)

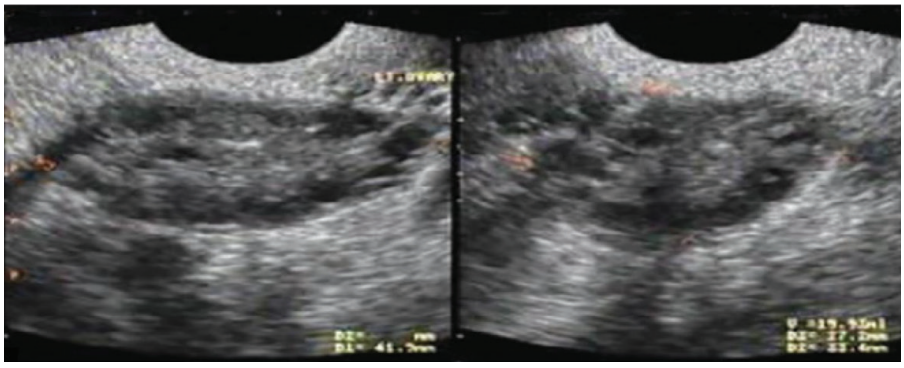

Fig. 5. An ultrasound image showing multiple mature follicles (≥ 18 mm) within the ovaries. These follicles would appear as round, dark (anechoic) cysts a (woman 39 years old; the 3rd day of the menstrual cycle)

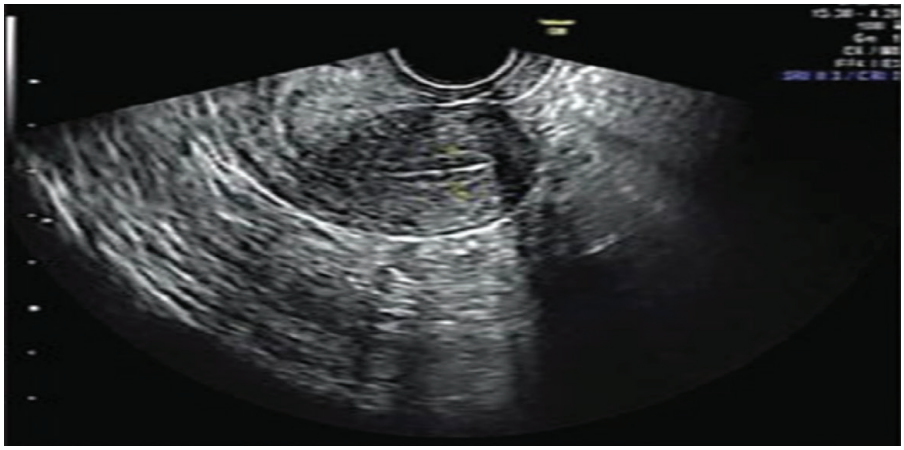

Fig. 6. An ultrasound image demonstrating a smooth and homogeneous endometrial pattern with a well-defined triple-line sign (echogenicity pattern) (a woman 29 years old; the 3rd day of the menstrual cycle)

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Table 5

Pregnancy Outcomes

Outcomes (n, %)	Treatment Group (LDN) (n = 175)	Control Group (n = 175)	p-value
Pregnancy rate	84 (48.0)	58 (33.0)	0.03
Implantation rate	79 (45.0)	51 (29.0)	0.02
Clinical pregnancy rate	75 (43.0)	53 (30.0)	0.01
Miscarriage rate	14 (8.0)	21 (12.0)	0.15

a negligible effect on FSH levels; the correlation is very weak and negative. There is thus only the most modest change in FSH between the treatment group (LDN) and control groups, which in turn indicates that LDN does not exert great influence over FSH regulation. On a similar note, LDN has a minimal effect on LH levels, with no significant differences observed between treatment and control groups. The weak negative correlation indicates LDN does not significantly change LH levels. The weak positive correlation with estradiol shows that although LDN treatment does cause a slight rise in this hormone's level, it is not great and is more of a variety only. Estradiol is essential for follicular development and maintenance of the uterine lining, but LDN's effect on these is minimal. LDN has a strong positive impact on progesterone levels. These levels are critical in preparing the endometrial lining for implantation. A higher progesterone level significantly enhances the likelihood of a successful pregnancy. This is one of the most pronounced effects of LDN treatment.

LDN treatment reduces NK cell activity, an essential change from elevated activity in NK cells linked with failed implantation. This strong negative correlation implies that LDN can effectively regulate the immune system to produce an environment conducive to pregnancy. LDN treatment significantly reduces ANA levels, which are often associated with autoimmune responses that hinder pregnancy. The moderate negative correlation shows that LDN helps to reduce autoimmune factors that could interfere with implantation. LDN has little to no effect on APA levels, as indicated by the very weak negative correlation. APA is another immune marker that can impact fertility, but the changes observed in this study are minimal. LDN significantly increases the pregnancy rate in women with RIF. This strong positive correlation indicates that LDN treatment substantially enhances the likelihood of achieving a pregnancy. LDN also improves the implantation rate, as evidenced by a strong positive correlation. This suggests that LDN enhances the chances of successful embryo implantation. The moderate to strong positive correlation between LDN and clinical pregnancy rates indicates that LDN improves the overall success of pregnancies, resulting in a higher clinical pregnancy rate. While the miscarriage rate in the treatment group is slightly lower than in the control group, the weak negative correlation suggests that LDN has a minor effect on reducing miscarriage rates, but this difference is not statistically significant (Table 6).

Based on the above correlations, it is clear that LDN treatment has a significant positive effect on several key parameters related to reproductive health. These include endometrial thickness, ovarian response, progesterone levels, immune regulation (NK cells and ANA), and pregnancy outcomes (implantation, clinical pregnancy rates, and pregnancy rates). The most notable effects are on immune markers (NK cells and ANA) and progesterone, which are crucial for successful implantation and pregnancy. However, LDN's impact on FSH, LH, estradiol, and APA is minimal. Overall, LDN appears to be a promising treatment for improving fertility outcomes in women with immunological infertility and RIF.

Numerous researches have examined the effects of naltrexone on reproductive health, including ovulation and pain control [20, 21], no previous research had yet investigated its potential benefits for those women whose RIF is due entirely to immunological processes. Therefore, our research is pioneering. It shows that LDN could be an effective medical intervention aimed at improving the reproductive outcome for this most difficult group of patients. The results we obtained indicated significant enhancements in numerous critical aspects: endometrial thickness, ovarian responsiveness, and immune modulation, all of which are vital parameters for a healthy pregnancy. The LDN treatment group showed a marked increase in endometrial thickness, the condition for optimal embryonic implantation as given by previous studies on endometrial receptivity [22, 23]. Furthermore, the higher grade of endometrial type observed in the LDN group suggests better receptivity of the uterus, an important condition for implantation success. That points to a lot of potential for LDN to be beneficially involved in the uterus, making a more welcoming spot for pregnancy. Greater ovarian response, which is indicated by more mature follicles, shows us that LDN may improve ovarian function and perhaps the quality of eggs as well. Although one cannot say this article proves conclusively about the eggs themselves, yet increased follicle number is in harmony with work by A. M. Fulghesu et al. on naltrexone and ovarian function in burdensome women [24]. This hints that LDN may help a woman with RIF to increase her endowment of eggs at the same time as restoring their reproductive capacity [24].

Another key finding of our study was the drop in immune markers, including NK cell and ANA. This drop is particularly significant because immune imbalance, such as disc-regulation of NK cell activity, is commonly associated with implantation failure [25]. LDN helps to regulate the immune system balance and thereby creates a more suitable environment for conception and childbirth. These encouraging findings imply that not only the immune system, but also other bodily systems are positively impacted by LDN. This could be the mechanism for why some women in our study have had better pregnancy outcomes. Prior to our study, most researches on naltrexone and ovulation had been directed towards its general effects thus far [26]. However, helping to

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Table 6

Correlation Coefficient between LDN and Various Parameters

Parameters	Correlation with LDN treatment (r)	Interpretation
Endometrial thickness (mm)	+0.85	Strong positive correlation: LDN significantly increases endometrial thickness, which is crucial for embryo implantation
Ovarian response (follicles ≥ 18 mm)	+0.80	Strong positive correlation: LDN improves ovarian response, as seen in the increased number of mature follicles
Endometrial pattern (grade)	+0.75	Moderate to strong positive correlation: LDN enhances the grade of the endometrial pattern, indicating improved uterine receptivity
FSH (mIU/mL)	–0.05	Very weak negative correlation: No significant change in FSH levels after LDN treatment, suggesting minimal impact
LH (mIU/mL)	–0.05	Very weak negative correlation: similar to FSH, LDN treatment has little to no impact on LH levels
Estradiol (pg/mL)	+0.10	Weak positive correlation: estradiol levels show a modest increase, but the effect of LDN is not substantial
Progesterone (ng/mL)	+0.90	Very strong positive correlation: LDN significantly increases progesterone levels, which is crucial for successful pregnancy
NK cells (%)	–0.75	Strong negative correlation: LDN reduces NK cell activity, which is linked to improved implantation success
ANA (mIU/mL)	–0.60	Moderate negative correlation: LDN reduces ANA levels, contributing to a more favorable immune environment for pregnancy
APA (mIU/mL)	–0.10	Very weak negative correlation: LDN has little to no impact on APA levels
Pregnancy rate (%)	+0.80	Strong positive correlation: LDN significantly increases pregnancy rates in women with RIF
Implantation rate (%)	+0.75	Strong positive correlation: LDN improves embryo implantation success
Clinical pregnancy rate (%)	+0.70	Moderate to strong positive correlation: LDN enhances clinical pregnancy rates
Miscarriage rate (%)	–0.15	Weak negative correlation: LDN treatment appears to slightly reduce miscarriage rates, but the effect is not statistically significant

Notes: FSH – follicle-stimulating hormone; LH – luteinizing hormone; NK – natural killer; ANA – antinuclear antibodies; APA – antiphospholipid antibodies.

replenish the stock of available evidence which indicates that naltrexone plays a key part in managing idiopathic (immunological) infertility and RIF is provided below.

Because our research is original, LDN could well act through various immunomodulatory mechanisms such as inflammation reduction and nurturing of a receptive uterus, all three of which are paramount in successful embryo implantation. The finding that women on LDN had an improved pregnancy rate supports the view that LDN helps to improve immune function and structure of the reproductive system. By doing so, it enhances the chances of a successful pregnancy.

Encouraging as these findings are, it should be noted that our current research is the first of its kind and further study is needed to verify the results in larger, more widespread patient populations. Subsequent studies could in turn consider both gaining a better understanding of the specific mechanisms through which LDN works to modulate immunity and of its impact on endometrial receptivity and ovarian function, as well as morphological and developmental changes.

Furthermore, long-term clinical studies are required to evaluate both the sustained safety and therapeutic efficacy of LDN in treating infertility, and to what length its effects are retained. In short, our research offers strong justification to believe that LDN may be of aid to women suffering from RIF and immunological infertility. This study, by bringing new perspectives to light on LDN's probable contribution to improved fertility outcomes, lays bare a vital area of future research endeavor. Continuing with our exploration of the effects of LDN may help us develop new and more powerful treatments for women suffering reproductive problems which stem from their immune systems.

CONCLUSIONS

The patients who had experienced RIF after the proposed treatment with LDN saw thriving changes in several key parameters, including endometrial thickness, ovarian response, and endometrial pattern factors, which are crucial for successful embryo implantation. In particular, when endometrial thickness rose to an ideal 9.8 mm in the group of patients who received LDN, against 7.6 mm seen with controls, this implies a more favorable uterine environment for nidation. Moreover, the increased ovarian response, reflected in a more significant number of mature follicles, lends support to the argument that LDN can have a beneficial effect on ovarian function, leading to possibly better quality of eggs and general IVF success. These findings are groundbreaking and offer a fresh look at LDN as a possible therapy for patients with immunological causes of RIF. By treating both immune dysfunction and reproductive parameters, LDN has achieved good results in increasing implantation as well as pregnancy rates among this difficult group of patients.

Since this is a first-of-its-kind study, it opens up the possibility for further research to confirm these results and explore LDNs broader applications in fertility treatment

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protocols. LDN needs to be developed as a medicine for immunological infertility. This would be particularly useful in those cases connected with elevated NK cells or other immune dysfunctions. Future research with larger groups of patients in differing clinical environments is necessary in order to fully understand the long-term efficacy and safety of LDN as a routine institutional treatment for RIF.

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