Cyclosporine A to Treat Unexplained Recurrent Spontaneous Miscarriage: Randomized, Controlled Trial

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Abstract

Background: Unexplained recurrent spontaneous miscarriage (URSA) accounts for up to 50–60% of recurrent pregnancy losses, with immune dysregulation playing a key pathogenic role. **Objective:** To assess the safety and effectiveness of cyclosporine A in enhancing pregnancy outcomes among women with unexplained recurrent spontaneous miscarriage.

Methods: This prospective, randomized, placebo-controlled trial included 78 women with URSA, randomly assigned (1:1) to receive either CsA (2–4 mg/kg twice daily) or placebo. Baseline clinical, laboratory, immunological, and ultrasonographic assessments were performed. Participants were followed through a screening phase, a one-year pre-pregnancy period, and up to 42 weeks after conception.

Results: No significant variances were observed in the timing of pregnancy loss, stillbirth, ectopic pregnancy, preterm birth, gestational age at delivery, neonatal anthropometric measures, sex, or maternal complications (all $P > 0.05$). Composite neonatal morbidity was lower in the Cyclosporine A group (17.9% vs. 25.0%) but didn't reach statistical significance ($P = 0.57$). Rates of individual neonatal adverse outcomes were also comparable between groups, with no increase in congenital anomalies or neonatal sepsis associated with Cyclosporine A treatment.

Conclusion: Cyclosporine A significantly reduced miscarriage rates and improved successful pregnancy outcomes in females with URSA without increasing maternal or neonatal adverse events, suggesting it may be an effective and safe therapeutic option in this population.

Keywords: Cyclosporine A; Unexplained recurrent spontaneous miscarriage; Immunomodulation; Pregnancy outcome

How to cite this article: Mohammed EM, Al-Rub MTG, Ibrahim EM, Mohammed HF, Galal AS. Cyclosporine A to treat unexplained recurrent spontaneous miscarriage: randomized, controlled trial. Int J Drug Deliv Technol. 2026;16(73s): 1429-1436. DOI: 10.25258/ijddt.16.73s.152

Introduction

Pregnancy loss (PL), defined as a spontaneous miscarriage occurring from conception until 20 weeks of gestation, is a frequent reproductive complication affecting approximately 1000–1500 per 10,000 pregnancies annually. Among these cases, nearly 1% are classified as recurrent pregnancy loss (RPL), representing a significant clinical and emotional burden for affected couples. **(1,2)**.

The etiology of RSA is complex and multifactorial. Established reasons comprise chromosomal abnormalities, uterine anatomical defects, endocrine disorders, and endometrial dysfunction. **(3)** Nevertheless, despite comprehensive clinical evaluation, the underlying cause remains unidentified in about 50–75% of cases. Increasing evidence suggests that maternal–fetal immune dysregulation plays a central role in the pathogenesis of unexplained RSA by disrupting immune tolerance at the maternal–fetal interface.**(4)** In addition to impairing reproductive outcomes, RSA has been associated with adverse psychological and cardiovascular consequences, highlighting the need for effective therapeutic interventions. **(5,6)**.

Several well-established risk factors have been recognized in females with recurrent spontaneous abortion (RSA). These include paternal chromosomal abnormalities, particularly reciprocal and Robertsonian translocations, infectious illnesses, endocrine disorders such as thyroid dysfunction, diabetes mellitus, and polycystic ovary syndrome, uterine structural anomalies, antiphospholipid antibody syndrome, and other autoimmune illnesses. **(7)**.

Despite advances in diagnostic evaluation, approximately 50–60% of recurrent pregnancy loss cases remain unexplained and are therefore classified as unexplained recurrent spontaneous abortion (URSA). **(7)** According to the World Health Organization (WHO), URSA is defined as the

occurrence of three or more consecutive spontaneous miscarriages prior to the 20th week of gestation. **(1,8).** The pathophysiological mechanisms underlying URSA are still poorly understood, limiting the development of effective therapeutic interventions. **(2)**Consequently, no universally accepted standard treatment currently exists for these patients. Clinical management is therefore largely empirical and primarily focuses on supportive care while researchers continue to investigate novel therapeutic strategies targeting the immunological and molecular mechanisms involved in pregnancy maintenance. **(8).** Management of RSA remains a major clinical challenge. Although numerous therapeutic strategies have been proposed, involving hormonal treatments, anticoagulants and immunomodulatory agents the effectiveness of these interventions remains controversial. Given the complex and frequently multifactorial nature of RSA, novel therapeutic approaches are urgently required to improve results of affected women.**(9)**.

Cyclosporine A (CsA) is a calcineurin inhibitor with potent immunosuppressive properties. It exerts its effect by binding to cyclophilin, forming a complex that inhibits calcineurin activity and suppresses T-cell activation and cytokine production, comprising IL-4, IFN-γ, and IL-2. Owing to its immunomodulatory effects, CsA has been commonly applied in organ transplantation and autoimmune illnesses, and more recently has been investigated as a potential therapeutic option for unexplained recurrent spontaneous miscarriage**(10–12).**

Patients and methods

A randomized, controlled experiment with 78 patients was performed with the following parameters: superior effectiveness; two arms; and a 1:1 placebo control. September 2022 marked the start of patient recruiting.

Sample Size

At first, it was estimated : 39 instances per group using Epi Info 3.

Criteria for inclusion: The following criteria must be satisfied by the participants before they may be included in the study: The following criteria must be met: you must be between the ages of 18 and 39, have had at least three episodes of spontaneous abortion, neither of your parents smoke, your male partner must have normal semen analysis results, and you must voluntarily participate in the clinical study with signed informed consent. Additionally, neither of your parents should have a history of any genetic diseases or chromosomal abnormalities. Participants were not allowed to participate if they met the following list of exclusion criteria: a history of infection, a problem with the immune system, a history of severe liver, heart, or kidney disease; a vaccine within the three months prior to study inclusion; a person's use of other investigational drugs or participation in other clinical researches within one month prior to study inclusion; a person's allergy to CsA or its ingredients; or a person whose participation was deemed inappropriate by the attending physician.

Methods

All patients were subjected to the following:

Thorough ;patient history collection and physical assessment. Personal details, menstruation and obstetric history (including the frequency and duration of miscarriages, the time between pregnancies, and the number of previous live births), current health status, medication use, food allergies, family medical history, and surgical and medical procedures performed in the past were all part of the history. The clinical evaluation included a thorough physical examination that included taking vital signs, measuring the patient's height, weight, and nutrition, and looking for indicators of abnormalities such as pale skin, swelling, rashes, or mucosal abnormalities. During the systemic examination, the patient's thyroid and lymph nodes were evaluated, along with their breasts, cardiovascular system, lungs, and abdomen. To identify conditions that could be contributing to the miscarriage, a comprehensive pelvic examination was carried out. This included a visual inspection of the external genitalia, a speculum examination of the vagina and cervix, and a bimanual assessment of the uterine position, size, and adnexal structures. Any masses, tenderness, or cervical motion tenderness were also evaluated.

Investigational Studies

Standard laboratory tests comprise complete blood count (CBC), hemoglobin A1C,albumin, coagulation profile (PT, PC, INR), liver enzymes (ALT-AST), total-direct bilirubin, human chorionic gonadotropin (β-HCG), urine analysis, inflammatory markers (CRP-ESR), glycosylated hemoglobin (HbA1C), and random blood glucose.

Scientific studies using radiological investigation: For the purpose of identifying and ruling out anatomical anomalies, all women who were eligible for the study received transvaginal and abdominal ultrasonography as part of the baseline screening. This was done for participants who experienced repeated spontaneous miscarriages.

Abdominal Ultrasound

For a non-invasive assessment of the pelvic and uterine tissues, abdominal ultrasonography was used. For the best possible view of the uterine architecture, examinations were planned for the early follicular phase (days 5-10) of the menstrual cycle. Supine

examinations were performed on patients with their bladders full to facilitate better pelvic organ delineation. A thorough review of the uterine size, shape, orientation, and the existence of fibroids, congenital malformations, or masses was part of the scanning routine. The ovarian size and morphology were also examined for cysts or follicles. The adnexal areas and pouch of Douglas were examined for masses or free fluid.

Transvaginal Ultrasound (TVUS)

To acquire precise pictures of the female reproductive systems, a gynecologist used transvaginal ultrasonography using a high-resolution transvaginal probe that ranged from 5 to 9 megahertz. A sterile, lubricated probe was delicately introduced into the vaginal canal after the patient was put in the lithotomy posture. The morphology of the ovaries and the growth of follicles were examined, as were any abnormal fluid collections, masses, or cysts in the pelvis, using real-time imaging. The uterine size, shape, and endometrial pattern were also evaluated.

Intervention Methods

Two weeks following the fertilization period, the serum β-human chorionic gonadotropin was tested. The experimental group was given cyclosporine A at a dosage of 2-4 mg/kg two times per day for six months if their β-HCG findings were positive, whereas the control group got a placebo that looked and felt the same for the same amount of time. There was a four-week screening and preparation period during which all participants were evaluated. Subsequently, they were followed up with at regular intervals during the study. After the screening, there was a one-year waiting period before treatment and participation may be ended in the event that pregnancy did not happen. Evaluation of the pregnancy began upon confirmation of pregnancy, with the start of gestational follow-up being marked as week zero.

Follow up

People participated in the study for a year before becoming pregnant after the screening phase ended. For as long as 42 weeks following conception, individuals underwent transvaginal ultrasonography every two weeks for the purpose of diagnosing miscarriage, monitoring embryonic development, or fetal heart activity. Fetal length and gestational sac size evaluated by ultrasonography were used to calculate gestational age in situations of pregnancy loss. Upon spontaneous abortion or delivery, all live-born newborns had a congenital anomaly examination by a doctor. Follow-up exams were then completed.

Outcome

A successful pregnancy was defined as a pregnancy that lasts for at least 20 weeks after treatment began, and this rate was the main endpoint of the study. Adverse pregnancy outcomes (such as preterm birth, stillbirth, and congenital abnormalities), miscarriage rate, live birth rate in the cyclosporine A-treated group, neonatal birth weight, and pregnancy-related complications (such as gestational diabetes mellitus, preeclampsia, bleeding, gestational hypertensive disorders, and thrombosis) were considered secondary products.

Ethical Considerations

The Research Ethics Committee gave its stamp of approval after reviewing the procedure. Patients were asked to provide their informed permission before they could be enrolled in the trial. Confidentiality of all data was maintained. Withdrawal from the research was completely voluntary and would not have any impact on participants' management.

Statistical Analysis

We used SPSS for Windows and Microsoft Excel 7 (Microsoft Corporation, NY, USA) to complete all of our statistical computations. SPSS comes from SPSS Inc. in Chicago, IL, USA and stands for "Statistical Package for the Social Sciences." The following tests were used to compare categorical data: salmon's exact test, linear by linear association, fisher's exact test, likelihood ratio, and chi square ($\chi 2$). If the p-value is greater than 0.05, it is considered non-significant (NS), if it is less than 0.05, it is considered significant (S), and if it is less than 0.01 there is a high level of significance (HS).

Results

Table (1): Patients Characteristics distribution in the examined groups

	Cyclosporine A group Number= 39	**Control group Number = 39**	**Test**	**P value**
Age (years) Mean ±SD	30.01 ± 3.26	29.25 ± 3.27	1.03	0.306
BMI Mean ±SD	21.64 ± 2.13	21.58 ± 3.48	0.08	0.932
Parity				
0	22 (56.4%)	26 (66.7%)	1.13	0.567
1	12 (30.7%)	8 (20.5%)		
2	5 (12.8%)	5 (12.8%)		
Number of previous miscarriages				
3	30 (76.9%)	28 (71.8%)	0.35	0.837

4	6 (15.4%)	8 (20.5%)		
5	3 (7.7%)	3 (7.7%)		

p value above 0.05: Not significant, P value under 0.05 is statistically significant, p-value under 0.001 is highly significant.

There was a statistically insignificant variance between the Cyclosporine A group and the control group with regard to age, BMI, parity and number of previous miscarriages P-value above 0.05. (Table 1)

Table (2): Pregnancy outcome distribution in the studied groups

	Cyclosporine A group Number = 39	**Control group Number = 39**	**Test**	**P value**
Miscarriage	10 (25.6%)	19 (48.7%)	5.81	**0.016 ***
Timing of Pregnancy Loss				
First trimester	4 (40%)	9 (47.4%)	0.144	0.70
Second trimester	6 (60%)	10 (52.6%)		
Successful pregnancy ≥20 weeks/ Live birth	28 (71.8%)	16 (41.02 %)	7.508	**0.006 ***
Stillbirth	1 (2.6%)	2 (5.1%)	0.35	0.556
Ectopic pregnancy	0 (0%)	2 (5.1%)	2.23	0.136
Among Live birth				
Preterm birth	5 (17.8%)	4 (25%)	0.64	0.722
Full term	23 (82.1%)	12 (75%)		

p value >0.05: Not significant, P value <0.05 is statistically significant, p<0.001 is highly significant.

Cyclosporine A group had a significantly lower miscarriage rate and higher rate of successful pregnancy ≥20 weeks/live birth compared to the control group ($p < 0.05$). Timing of pregnancy loss and other pregnancy outcomes, including stillbirth, ectopic pregnancy, and preterm birth, showed a statistically insignificant variances among groups. (Table 2)

Table (3): Neonatal outcome full term delivery distribution in the studied and control groups

	Cyclosporine A group Number = 23	**Control group Number = 12**	**Test**	**P value**
Gestational age delivery (weeks) Mean ±SD	38.48 ± 1.92	38.75 ± 1.12	0.51	0.610
Birth weight (kg) Mean ±SD	3.16 ± 0.53	2.91 ± 0.66	1.4	0.167
Birth height (cm) Mean ±SD	50.44 ±2.52	49.07 ±2.45	1.84	0.071
Sex				
Male	11 (47.8%)	2 (16.7%)	3.27	0.07
Female	**12 (52.2%)**	**10 (83.3%)**		

p value above 0.05: Not significant, P value under 0.05 is statistically significant, p-value under 0.001 is highly significant.

There were a statistically insignificant variances among the Cyclosporine A and control groups regarding gestational age delivery, birth weight, birth height and Sex P>0.05. (Table 3)

Table (4): Maternal outcome distribution in the studied groups

	Cyclosporine A group Number = 39	**Control group Number = 39**	**Test**	**P value**
Postpartum complications	6 (15.4%)	7 (17.9 %)	0.09	0.76

Types of postpartum complications				
Preeclampsia	2 (5.1%)	3 (7.7%)	0.01	0.902
GDM	1 (2.6%)	0 (0%)	1.03	0.314
Gestational HTN	2 (5.1%)	3 (7.7%)	0.214	0.643
Postpartum hemorrhage	1 (2.6%)	1 (2.6%)	0	1

There were a statistically insignificant variances between the Cyclosporine A and control groups regarding prevalence of Preeclampsia, GDM, Gestational HTN and Postpartum hemorrhage. (Table 4)

Table (5): Comparison of Composite Neonatal Morbidity Between the Cyclosporine A and Control Groups

Outcome	Cyclosporine A group (Number=28)	Control group (Number =16)	Test	P value
Composite Neonatal Morbidity				
Present	5 (17.9%)	4 (25%)	0.31	0.57
Absent	23 (82.1%)	12 (75%)		

Composite neonatal morbidity was observed in 17.9% of neonates in the Cyclosporine A group compared with 25% in the control group. Although the incidence was lower in the Cyclosporine A group, the variance was statistically insignificant (P = 0.57). This finding suggests that Cyclosporine A administration wasn't associated with a significant effect on the overall rate of composite neonatal morbidity compared to the control group. (Table 5)

Table (6): Comparison of Individual Neonatal Outcomes Between the Cyclosporine A and Control Groups

Outcome	Cyclosporine A group (Number =28)	Control group (Number =16)	Test	P value
Preterm delivery (<37 weeks)	5 (17.9%)	4 (25%)	0.31	0.57
Low birth weight (<2500 g)	1 (3.6%)	1 (6.25%)	0.03	0.85
SGA (<10th percentile)	0 (0%)	1 (6.25%)	1.41	0.23
NICU admission	2 (7.1%)	1 (6.25%)	0.01	0.90
Respiratory distress	1 (3.6%)	0 (0%)	0.9	0.34
Neonatal sepsis	0 (0%)	0 (0%)	-	-
Jaundice requiring treatment	1 (3.6%)	1 (6.25%)	0.03	0.85
Congenital anomalies	0 (0%)	0 (0%)	-	-

p value >0.05: Not significant, P value <0.05 is statistically significant, p<0.001 is highly significant.

There were a statistically insignificant variances between the Cyclosporine A and control groups regarding any of the assessed neonatal outcomes (all P > 0.05). Rates of preterm delivery, low birth weight, NICU admission, respiratory distress, and jaundice requiring treatment were comparable between both groups. SGA was reported in one neonate in the control group and none in the Cyclosporine A group, without reaching statistical significance. No cases of neonatal sepsis or congenital anomalies were observed in either group. These findings indicate that Cyclosporine A treatment was not associated with an elevated risk of adverse neonatal outcomes

Discussion

The current study showed that there was a statistically insignificant variance between the Cyclosporine A group and the control group regarding age, BMI, parity and number of previous miscarriages. This indicates that both groups were comparable at baseline, minimizing the potential influence of confounding demographic and obstetric variables on the study outcomes. Therefore, the observed differences in pregnancy outcomes are more likely attributable to the therapeutic effect of Cyclosporine A rather than baseline differences between the study groups.

These findings are consistent with those reported by **Wang et al., (8),** who found no significant variances between the Cyclosporine A and control groups regarding maternal age, BMI, reproductive history, or previous pregnancy losses before treatment initiation. Similarly, the systematic review and network meta-analysis by **Zhang et al. (12)** concluded that baseline demographic and obstetric characteristics were generally well balanced across the included randomized studies, supporting the validity of treatment comparisons.

The present study demonstrated that Cyclosporine A group had a significantly reduced miscarriage rate and higher rate of successful pregnancy ≥20 weeks/live birth compared to the control group ($p < 0.05$). Timing of pregnancy loss and other pregnancy outcomes, including stillbirth, ectopic pregnancy, and preterm birth, showed no statistically significant differences between groups. These findings suggest that Cyclosporine A may improve pregnancy maintenance by enhancing maternal–fetal immune tolerance and reducing excessive maternal immune responses that contribute to recurrent pregnancy loss.

The higher live birth rate observed in the Cyclosporine A group is also consistent with the findings of **Ling et al., (13)** who stated that low-dose Cyclosporine A significantly increased the live birth rate in women with unexplained recurrent spontaneous abortion without increasing maternal or fetal adverse effects. These findings support the hypothesis that immunomodulation by Cyclosporine A enhances fetal survival throughout pregnancy.

Similar findings were reported by **Azizi et al., (14)** who observed that Cyclosporine A therapy improved pregnancy outcomes and increased the probability of successful pregnancy in women with recurrent pregnancy loss associated with elevated Th1/Th2 ratios.

Regarding the timing of pregnancy loss, a statistically insignificant variance was observed among the two groups in either first- or second-trimester miscarriages ($P = 0.70$). This finding indicates that although Cyclosporine A reduced the overall incidence of miscarriage, it did not significantly influence the gestational age at which pregnancy loss occurred. This may indicate that although Cyclosporine A reduces the overall risk of pregnancy loss, it does not appear to influence the gestational age at which miscarriage occurs once pregnancy loss has been initiated.

Our result revealed that there were a statistically insignificant variances between the Cyclosporine A and control groups regarding gestational age delivery, birth weight, birth height and Sex. This may indicate that the beneficial effect of Cyclosporine A is primarily related to enhancing maternal–fetal immune tolerance during early pregnancy rather than influencing fetal growth or neonatal development.

In agreement with , **Hu et al.,(9)** reported in their systematic review and network meta-analysis that Cyclosporine A improved pregnancy outcomes without increasing adverse neonatal or obstetric outcomes. The authors concluded that CsA was not related to an elevated risk of preterm delivery, low birth weight, congenital anomalies, or other unfavorable neonatal outcomes, supporting its safety profile in women with recurrent spontaneous abortion.

In the current research, although the proportion of male neonates was higher in the Cyclosporine A group than in the control group (47.8% vs. 16.7%), the variance wasn't statistically significant ($P = 0.07$). Since neonatal sex is genetically determined and is not expected to be influenced by immunomodulatory therapy, this difference is most likely attributable to random variation rather than an effect of Cyclosporine A.

Our study demonstrated that there were a statistically insignificant variances between the Cyclosporine A and control groups regarding prevalence of Preeclampsia, GDM, Gestational HTN and Postpartum hemorrhage. These findings suggest that short-term administration of low-dose Cyclosporine A during early pregnancy is generally well tolerated and doesn't appear to increase the risk of maternal pregnancy-related complications.

In accordance with , **Hu et al.,(9)** in their systematic review and network meta-analysis, concluded that Cyclosporine A significantly improved pregnancy outcomes without increasing maternal adverse events, supporting its favorable maternal safety profile in women with recurrent spontaneous abortion.

The maternal safety observed in the current study is also consistent with the results of **Ling et al., (13)** who reported that treatment with low-dose Cyclosporine A improved pregnancy outcomes without increasing the incidence of maternal complications or congenital abnormalities. These findings suggest that short-term administration of Cyclosporine A during early pregnancy is generally well tolerated and may represent a safe immunomodulatory therapeutic option for women with unexplained recurrent spontaneous miscarriage.

Our result showed that composite neonatal morbidity occurred in 17.9% of neonates in the Cyclosporine A group compared with 25% in the control group. Although the incidence was lower among neonates born to mothers who received Cyclosporine A, the variance didn't reach statistical significance ($P = 0.57$). These findings indicate that Cyclosporine A treatment was not related to a significant reduction in the overall rate of composite neonatal morbidity compared with the control group. The absence of a significant difference suggests that although Cyclosporine A improves pregnancy continuation, it does not adversely affect the overall neonatal health status after birth.

In alignment with, **Hu et al.,(9)** reported that Cyclosporine A significantly improved pregnancy outcomes without increasing neonatal complications, indicating a favorable neonatal safety profile.

The neonatal safety observed in the current study is also supported by **Zhang et al. (12)**, who demonstrated that treatment with Cyclosporine A in

women with recurrent spontaneous abortion improved pregnancy outcomes without increasing the frequency of neonatal adverse events or congenital abnormalities. These findings further support the safety of short-term low-dose Cyclosporine A during pregnancy.

Similarly, **Ling et al., (13)** reported that low-dose Cyclosporine A therapy improved live birth rates without increasing neonatal complications, suggesting that the immunomodulatory effects of Cyclosporine A enhance pregnancy success while maintaining an acceptable neonatal safety profile.

Our result demonstrated that a statistically insignificant variances were observed between the Cyclosporine A and control groups regarding neonatal outcomes (all $P > 0.05$). Rates of preterm delivery, reduced birth weight, NICU admission, respiratory distress, and jaundice requiring treatment were comparable between the two groups. No cases of neonatal sepsis or congenital anomalies were reported, suggesting that Cyclosporine A was not related to an increased risk of adverse neonatal outcomes. These findings further support the neonatal safety of Cyclosporine A, indicating that its immunomodulatory effects throughout pregnancy don't appear to increase the risk of adverse neonatal outcomes or impair neonatal adaptation after birth.

These findings were reported by **Cavalcante et al.,(15)** who concluded that calcineurin inhibitors, including Cyclosporine A, did not increase neonatal adverse outcomes or congenital malformations.

Furthermore, **Zhang et al. (12)**, demonstrated that treatment with Cyclosporine A improved pregnancy outcomes without compromising neonatal safety, while the recent meta-analysis by **Hu et al.,(9)** confirmed that Cyclosporine A-based therapy was associated with improved pregnancy outcomes and didn't rise the incidence of adverse neonatal events.

Despite the favorable clinical outcomes and safety profile observed in the current research, the clinical application of Cyclosporine A (CsA) in females with unexplained recurrent spontaneous abortion (URSA) remains a subject of ongoing debate within the wider literature. Recent systematic reviews and network meta-analyses have raised critical reservations regarding the generalized efficacy of immunomodulatory interventions.

Specifically, a comprehensive network meta-analysis by **Wang et al., (8)** evaluating therapeutic interventions for idiopathic recurrent pregnancy loss (RPL) concluded that no single intervention demonstrated a statistically significant capacity to improve live birth rates or reduce miscarriage risk. This perspective aligns with an earlier systematic review and meta-analysis by **Vater et al.,(16),** which similarly concluded that there remains insufficient high-quality evidence to recommend standard medical or immunosuppressive therapies, such as CsA, for idiopathic RPL.

Beyond secondary literature analyses, this conservative clinical stance is strongly reflected in current major international guidelines. The American Society for Reproductive Medicine (ASRM) Committee Opinion **Gracia et al., (17)** explicitly advises against routine immune testing and the clinical deployment of immunomodulatory therapies for RPL outside of strictly controlled research protocols, citing the poor quality and limited scale of historical clinical trials. Crucially, however, it must be emphasized that these opposing viewpoints and institutional guidelines do not stem from direct randomized controlled trials demonstrating a definitive lack of efficacy or therapeutic failure for CsA. Instead, the core consensus among these skeptical bodies focuses on the premise that the existing body of literature is structurally inadequate and lacks the rigorous, large-scale, multi-center randomized controlled trials (RCTs) required to establish universal clinical protocols. Therefore, the findings of our study provide vital, prospective clinical evidence that directly addresses this gap in the literature, demonstrating the tangible benefits of targeted CsA therapy under proper clinical observation.

Conclusion

Cyclosporine A significantly reduced the rate of miscarriage and improved successful pregnancy outcomes, including pregnancy beyond 20 weeks and live birth, in women with unexplained recurrent spontaneous miscarriage. In contrast, Cyclosporine A had no significant effect on the timing of pregnancy loss, obstetric complications, neonatal characteristics, composite neonatal morbidity, or other neonatal outcomes. Importantly, no increase in adverse maternal or neonatal outcomes was observed, suggesting that Cyclosporine A is an effective and relatively safe therapeutic option for improving pregnancy outcomes in females with unexplained recurrent spontaneous miscarriage. Nevertheless, larger multicenter studies with longer follow-up are recommended to further confirm its long-term efficacy and safety.

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