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BRIEF REPORT

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Use of oral allylestrenol in women with recurrent spontaneous abortion: A retrospective clinical trial

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Abstract: Recurrent spontaneous abortion (RSA), defined as two or more clinically confirmed pregnancies that end before 20-24 weeks of gestation, encompasses both embryonic and fetal losses and is a significant clinical challenge. The aim of this study was to compare the efficacy of allylestrenol (AT) and progesterone in improving pregnancy outcomes in RSA. From June 2021 to June 2024, 480 participants were randomly assigned to an AT, Progesterone, or Control group. Key outcomes included early pregnancy rates, ongoing pregnancies with fetal heart activity, live birth rates after 24 weeks, and pregnancy loss before 24 weeks. Results indicated significantly higher pregnancy rates at 6-8 weeks in both the Allylestrenol (71.8%) and Progesterone groups (76.2%) compared to the Control group (57.5%). At 12 weeks, ongoing pregnancies with fetal heart activity were higher in the Allylestrenol (65%) and Progesterone groups (64%) versus the Control group (52.5%). Both treatment groups had higher live birth rates (60% and 60.6%) compared to the Control group (45%). Pregnancy loss before 24 weeks was lower in both treatment groups (31.8% and 33.1%) compared to the Control group (38.7%). No significant adverse reactions were observed, indicating good safety profiles for both treatments. These findings suggest that both treatments effectively improve pregnancy outcomes in cases of RSA with satisfactory safety, supporting their potential clinical use. However, further research is needed to explore their long-term effects and broader applicability in clinical settings.

***Keywords*:** recurrent spontaneous abortion, allylestrenol, progesterone, live birth rate

Introduction

Recurrent spontaneous abortion (RSA) is characterized by the occurrence of two or more clinically confirmed pregnancies that end before 20-24 weeks of gestation (*1*), encompassing both embryonic and fetal losses; RSA occurs in approximately 1% to 2% of couples attempting to conceive (*2*). The causes of RSA are diverse and may involve genetic abnormalities (*3*), uterine anatomical issues (*4*), hormonal imbalances (*5*), immune system disorders (*6*), and coagulation dysfunctions (*7*). To effectively manage RSA, a thorough evaluation to identify underlying causes and provide tailored treatment is essential. This may include genetic testing, hormonal therapy, corrective surgery for uterine abnormalities, immunomodulatory therapy, and lifestyle adjustments.

Progesterone has shown potential benefits in cases of recurrent spontaneous and threatened abortions (*8*). Progesterone prepares the uterine environment for embryo implantation and sustains pregnancy (*9*). Nevertheless, the use of progesterone to prevent miscarriages remains a topic of debate, given that the optimal dosing and timing have yet to be definitively established (*10*). Continued research is crucial to comprehensively understanding progesterone's role in pregnancy outcomes and to formulate effective strategies to prevent miscarriages.

Allylestrenol (AT) is a promising therapeutic option used to address conditions such as miscarriage (*11*) and preterm labor (*12*). The aim of the current study was to evaluate the effectiveness and safety of AT in the treatment of threatened miscarriages. Through a retrospective clinical trial conducted during the first trimester in women with RSA, this study sought to compare pregnancy rates, miscarriage rates, and live birth rates between a group receiving oral AT, a group

receiving progesterone treatment, and a control group. The hypothesis posited that oral administration of AT would lead to a reduction in miscarriage rates and an increase in live birth rates among women with RSA. The results of this study are expected to provide valuable insights into the potential benefits of AT in preventing miscarriages and enhancing pregnancy outcomes for women with RSA. However, further research and additional clinical trials are necessary to validate and expand upon these initial findings.

Patients and Methods

Types of study

A retrospective cohort study was conducted at the Obstetrics and Gynecology Hospital of Fudan University, with approval from the hospital's ethics committee (No. 2019-57). This clinical trial evaluated the use of AT and progesterone in women with RSA and it adhered to the principles of the Declaration of Helsinki and Good Clinical Practice guidelines (*13*). All participants provided informed consent, and stringent measures were taken to protect their confidentiality and privacy.

Participants

Inclusion criteria: *i*) Age 20 to 40; *ii*) Body mass index (BMI) of 18-30 kg/m²; *iii*) Diagnosed with RSA; *iv*) No contraindications to continuing the pregnancy; and *v*) Normal results on chromosomal and genetic tests.

Exclusion criteria: *i*) Patients with abnormal heart, liver, lung, or kidney function, with psychiatric disorders, or tumors; *ii*) A history of chromosomal abnormalities in one's parents; *iii*) Structural abnormalities of the uterus and fallopian tubes; and *iv*) Male factor.

Intervention

Patients were administered oral AT or progesterone at a dosage of 10 mg twice daily starting from day 18-20 of the menstrual cycle. Participants were instructed to engage in clinic-directed intercourse as per the physician's guidance. Upon a positive pregnancy test, the dosage of oral AT or progesterone was increased to 10 mg three times daily, continuing until 12 weeks of gestation. During this period, ultrasound scans and blood tests were performed as necessary to monitor treatment progress and evaluate treatment efficacy up to the 12-week gestation mark.

Outcome measures

The purpose of this study was to evaluate pregnancy outcomes, including the pregnancy rate at 6-8 weeks, ongoing pregnancy with fetal heart activity at 12 weeks, the live birth rate after 24 weeks of gestation, pregnancy loss before 24 weeks of gestation, and adverse drug reactions.

Statistical analysis

The live birth rate in the progesterone treatment group was 65.8%, as observed in a randomized double-blind clinical trial. Previous research has suggested that the live birth rate could potentially exceed 70% with AT treatment (*14*). To determine the study's sample size, various parameters were considered, including a significance level of $\alpha = 0.05$, a power of $\beta = 0.1$, a test validity of 0.9, and a 5% loss to follow-up rate. Moreover, this study noted a miscarriage rate of 32.2% in the progesterone treatment group, with 50% of those cases demonstrating chromosomal abnormalities in the embryos, corresponding to 16.1% of the total sample size of 160 patients per group. For clinical trials, continuous variables with a normal distribution were verified using the Kolmogorov-Smirnov test. Data were expressed as the mean ± standard deviation and analyzed using one-way analysis of variance (ANOVA). If the data did not follow a normal distribution, they were expressed as the median (interquartile range) and analyzed using the Kruskal-Wallis test. Categorical variables were expressed as percentages and analyzed using the Pearson χ^2 test.

Results and Discussion

This study provides compelling evidence that both AT and progesterone are effective in enhancing pregnancy outcomes among women with RSA. The improved pregnancy and live birth rates observed across these treatments underscore the clinical potential of hormone-based therapies in managing RSA. To fully understand the implications of these findings, however, one must delve into the underlying physiological and pharmacological mechanisms. For instance, exploring how these hormones support embryo implantation and early development can elucidate their roles in improving outcomes. Additionally, a comparison with similar studies in the literature would provide valuable context, revealing both consistencies and divergences that could inform the direction of future research.

Participants' demographic information and baseline characteristics

Between June 2021 and June 2024, 508 women were screened, and 480 participants ultimately met the inclusion criteria and completed the study (Figure 1). Baseline characteristics, such as age and BMI, were statistically similar across the three groups, with no significant differences in age ($p = 0.46$) or BMI ($p = 0.96$) (Table 1). This demographic comparability is essential, as it reduces the likelihood that observed outcomes are due to confounding variables rather than treatment

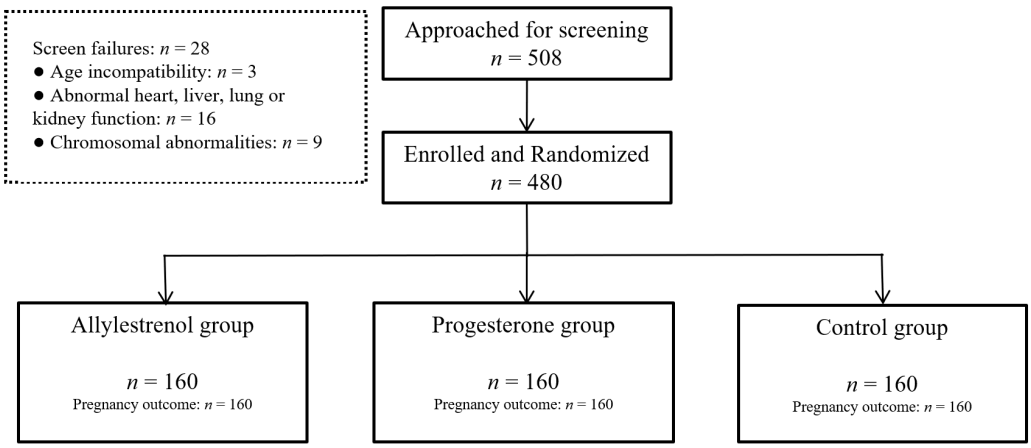

Figure 1. Overview of the study and randomization.

Table 1. The baseline characteristics of women with RSA

	Allylestrenol group (n = 160)	Progesterone group (n = 160)	Control group (n = 160)	p value
Age of women (years)	32.18 ± 1.2	32.09 ± 3.4	32.47 ± 3.1	0.46
BMI (kg/m^2)	21.40 ± 2.8	20.47 ± 1.9	21.51 ± 2.6	0.96
Number of previous miscarriages				
0	22	25	24	0.06
1	72	76	73	0.05
2	55	51	50	0.55
≥ 3	11	8	13	0.11

Abbreviations: BMI: body mass index.

effects. Such baseline uniformity ensures that differences in outcomes can be more confidently attributed to the interventions themselves. This rigor in patient selection aligns with best practices in clinical research, providing a solid foundation for the study's conclusions by enhancing internal validity and reducing potential biases.

Pregnancy rate at 6-8 weeks

The pregnancy rate at 6-8 weeks was notably higher in both the AT group (71.8%) and the Progesterone group (76.2%) compared to the Control group (57.5%) ($p < 0.0001$). These findings suggest both treatments provide critical hormonal support during early pregnancy. Further investigation into the mechanisms by which these hormones influence implantation could deepen our understanding. The slightly higher rate observed with progesterone, while not statistically significant, may indicate a potential advantage that warrants further exploration. Progesterone, known for its role in maintaining the luteal phase and promoting endometrial receptivity, has been widely studied in various conditions related to pregnancy maintenance. For instance, in patients undergoing *in vitro* fertilization (IVF), progesterone supplementation has been shown to significantly improve implantation rates and pregnancy outcomes (*15*). Similarly, AT has been used to treat threatened miscarriage and preterm labor, demonstrating efficacy in sustaining early pregnancies (*16*). Further research into the underlying mechanisms of these treatments, and particularly their effects on implantation, could deepen our understanding of their role in early pregnancy support.

Ongoing pregnancy with fetal heart activity at 12 weeks

At 12 weeks, ongoing pregnancies with detectable fetal heart activity were reported in 65% of the AT group and 64% of the Progesterone group, both of which were significantly higher than in the Control group (52.5%) ($p < 0.0001$). These results suggest comparable efficacy in sustaining pregnancies during this crucial early stage. Analyzing the physiological pathways involved could provide insights into how these treatments contribute to ongoing viability. The comparable outcomes observed in both the AT and Progesterone groups suggest that AT may offer similar benefits in promoting pregnancy viability, and particularly in women with a history of recurrent miscarriage. Although these results revealed no significant differences between AT and progesterone, the slightly higher ongoing pregnancy rate in the Progesterone group warrants further exploration, especially considering the possibility of nuanced differences in patient response or long-term outcomes.

Live birth rate after 24 weeks of gestation

The live birth rate after 24 weeks of gestation was 60% (96/160) for the AT group and 60.6% (97/160) for the Progesterone group, both of which were significantly higher than the 45% (72/160) observed in the Control group ($p < 0.0001$). This highlights the effectiveness of both treatments in facilitating live births beyond this critical threshold. Progesterone is considered a key physiological component for embryo implantation and maintaining pregnancy. It plays a crucial role in preparing the endometrium for implantation, suppressing uterine contractions, and promoting placental development. The importance of progesterone in early pregnancy is well-documented, as it stabilizes the uterine lining and supports the growing embryo. The removal of the corpus luteum, which is the primary source of progesterone in early pregnancy, or the use of progesterone antagonists such as mifepristone, can lead to pregnancy termination (*17*). Women with a history of miscarriage who experience bleeding in early pregnancy may benefit from the use of vaginal progesterone. Vaginal micronized progesterone, typically administered at a dosage of 400 mg twice daily, is associated with increased live birth rates (*18*). Comparative analyses with other studies involving similar treatments could enhance our understanding of the broader implications of these findings.

Pregnancy loss before 24 weeks of gestation

Pregnancy loss before 24 weeks was significantly lower in both treatment groups compared to that in the Control group. The AT group had a loss rate of 31.8% (51/160), while the Progesterone group had a rate of 33.1% (53/160), both of which were lower than 38.7% (62/160) in the Control group ($p = 0.0011$). These findings underscore the effectiveness of both treatments in reducing early pregnancy losses, with no significant differences between the two treatments.

In summary, both AT and progesterone significantly improve key pregnancy outcomes, including higher early pregnancy rates, increased ongoing pregnancies with fetal heart activity, and live births, while reducing losses before 24 weeks. These results indicate that both treatments are viable, effective options for enhancing pregnancy success among women with RSA (Table 2).

Adverse reactions

The incidence of adverse reactions, including nausea, vomiting, headaches, and dizziness, was similar across the AT, Progesterone, and Control groups, with no statistically significant differences. This suggests that both treatments are well-tolerated, providing reassurance regarding the safety of prolonged hormonal support in RSA management. The similar adverse reaction profiles imply that AT offers a comparable safety margin to progesterone, thus supporting its clinical utility as a potential alternative in cases where progesterone is less well-tolerated or contraindicated (Table 3).

The safety profile of both agents further supports their use as long-term interventions in this high-risk population, as tolerability is a crucial consideration in the sustained management required for patients with RSA. This comparable tolerability aligns with prior research on the use of progestational agents in pregnancy, providing further evidence that these treatments can be safely used without having significant adverse effects.

Conclusion

Our findings indicate that both AT and progesterone significantly enhance pregnancy outcomes compared to those in the Control group. The pregnancy rate at 6-8 weeks was markedly higher in the treatment groups, with AT resulting in a rate of 71.8% and progesterone resulting in one of 76.2%, both of which significantly exceeded 57.5% in the Control group ($p < 0.0001$). This suggests that both treatments are effective in increasing

Table 2. Pregnancy outcomes

Outcomes	Allylestrenol group (%)	Progesterone group (%)	Control group (%)	*p* value
Pregnancy rate at 6-8 weeks	115/160 (71.8)	122/160 (76.2)	92/160 (57.5)	< 0.0001
Ongoing pregnancy with fetal heart activity at 12 weeks	104/160 (65.0)	102/160 (64.0)	84/160 (52.5)	< 0.0001
Live birth rate after 24 weeks of gestation	96/160 (60.0)	97/160 (60.6)	72/160 (45.0)	< 0.0001
Pregnancy loss before 24 weeks of gestation	51/160 (31.8)	53/160 (33.1)	62/160 (38.7)	0.0011

Table 3. Adverse reactions during pregnancy

	Allylestrenol group ($n = 160$)	Progesterone group ($n = 160$)	Control group ($n = 160$)	*p* value
Nausea and vomiting	11	10	13	0.25
Headache	8	6	9	0.36
Dizziness	13	12	11	0.76

early pregnancy success.

These findings demonstrate that AT significantly enhances the clinical pregnancy rate and live birth rate while reducing the miscarriage rate compared to rates in the Control group. These results suggest that AT could potentially become a new standard medication for treating patients with RSA. Previous research has also corroborated the use of progesterone in preventing multiple pregnancies and associated complications, such as maternal, fetal, and neonatal morbidity and mortality (*19*). However, the use of progestogens in threatened miscarriage treatment remains controversial, with conflicting study results regarding its impact on reducing miscarriage rates (*20*). Consequently, there is an ongoing necessity for quality, large-scale studies to ensure the safety and appropriateness of medications administered to pregnant women (*21*).

The current findings indicate that both AT and progesterone are effective at improving key pregnancy outcomes, including early pregnancy rates, ongoing pregnancies with fetal heart activity, live birth rates, and reducing pregnancy loss before 24 weeks. Moreover, both treatments are well-tolerated with no significant differences in adverse reactions. These results suggest that either AT or progesterone can be considered a viable option for enhancing pregnancy success in clinical settings. Further research could delve into the long-term effects and potential benefits of these treatments in diverse populations.

In essence, oral AT has demonstrated the potential to reduce the risk of miscarriage in women experiencing preterm abortion during early pregnancy. However, further research, and particularly with larger sample sizes, is warranted to evaluate its impact on live birth rates, obstetric complications, and potential adverse drug reactions. Conducting comprehensive studies in these domains will be critical to establishing a more comprehensive understanding of the efficacy and safety of oral AT as a treatment for preterm abortion.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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