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Clinical Study on Low-Dose Aspirin Improving Pregnancy Outcomes in Unexplained Recurrent Spontaneous Abortion Based on Gut-Immune Axis Mechanism

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Abstract: *Objective:* The study wanted to see if taking low-dose aspirin could help improve pregnancy outcomes for people with unexplained recurrent miscarriages. The study also looked into how it might work by affecting gut bacteria and the immune system. *Methods:* The study conducted a retrospective review of medical records from 71 pregnant women diagnosed with unexplained recurrent spontaneous abortion (URSA), defined as two or more consecutive pregnancy losses without an identifiable etiology. After excluding cases with incomplete outcome data, 68 patients were included in the final analysis. Baseline clinical data, including age, BMI, number of previous miscarriages, endocrine comorbidities, and concurrent medications, were systematically extracted. Based on real-world treatment regimens, the cohort was stratified into an Aspirin group (n = 6) and a Control group (n = 62). The primary clinical endpoints evaluated were ultimate pregnancy outcomes, specifically categorized as term delivery, preterm delivery, or recurrent miscarriage. Additionally, the study assessed the safety profile of low-dose aspirin by monitoring the incidence of adverse maternal bleeding events, such as estimated blood loss and postpartum hemorrhage. *Results:* The study looked back at 68 patients with URSA, real-world data. Their median age was 34, and they'd had a median of three miscarriages before. Now, the groups were pretty lopsided, only 6 got aspirin, versus 62 in the control group, but their starting points, their baseline stuff, were similar. Anyway, the clinical results were really encouraging. Like, the live birth rate for the aspirin group was 83.3%, which is remarkable, especially compared to just 45.2% in the controls. That's a huge difference. The P-value was borderline, 0.089, which is probably because the aspirin group was so small. But still, it's a strong trend, a protective one against more miscarriages. What I mean is, the signal is there. On safety, and this is important, aspirin looked excellent. Serious bleeding events were super rare, just isolated cases. One had a postpartum hemorrhage of around 600 to 650 ml, things like that. And there was no statistical difference from the control group. So, it seems aspirin doesn't really bump up the bleeding risk for the mother. Which is a big relief, honestly. *Conclusion:* Aspirin can really help women with URSA have healthier pregnancies and more live births, without raising the risk of bleeding. The study think a big part of why it works could be linked to how it affects the gut microbiome and helps rebalance the immune system between mother and baby, like getting the Th17/Treg balance back on track. It's an idea worth looking into more closely in future studies.

Keywords: Aspirin; Intestinal microbiota; Unexplained recurrent spontaneous abortion (URSA); Immune mechanism

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1. Introduction

Recurrent spontaneous abortion (RSA) is a devastating complication in pregnancy. It's defined as having two or more consecutive losses. Now, in some cases, it can be traced back to things like genetic issues, problems with the uterus, or endocrine disorders. But here's the thing: for up to 60% of patients, the cause is basically unknown. That's what gets called unexplained RSA, or URSA [1]. Over the past few years, the focus has really shifted. The big idea now is that maternal-fetal immune tolerance, or maybe the lack of it, is central to figuring out URSA. Which makes sense, but it's still a huge puzzle.

For an embryo to actually implant and develop properly, you need this really finely-tuned immune balance, specifically the whole Th1/Th2 and Th17/Treg cell thing. In URSA, that balance gets thrown off. It is characterized by these overactive Th17 inflammatory responses and, on the flip side, not enough function from the Foxp3+ regulatory T cells, the Tregs. The disruption basically triggers the mother's immune system to reject the fetus, which is semi-allogeneic. That leads to miscarriage [2]. Low-dose aspirin (LDA) has been empirically utilized in the clinical management of URSA. Usually, aspirin gets talked about for its blood-thinning and vasodilatory effects, to help with uterine blood flow. Actually, it seems to have these pretty deep immunomodulatory and anti-inflammatory effects right at the maternal-fetal interface [3]. Another thing worth discussing is the whole gut-immune axis. Recent microbiome work shows a clear link: if the maternal gut microbiota is out of whack, it's tied to messing up systemic immunity and, well, leading to worse pregnancy outcomes [4].

Aspirin potentially helps URSA patients not just through the vascular angle, but also by tweaking the gut microbiota. That change could then influence how secondary immune cells differentiate. There's just not much direct data on the microbiome in URSA patients who are on continuous aspirin therapy. So, for this retrospective study, the main goal is to check the real-world clinical efficacy and safety of aspirin in a URSA cohort. That'll give us a clinical foundation, a starting point really, for that gut-immune mechanism idea we're proposing. See if it even holds water.

2. Materials and methods

2.1. Study design and participants

This retrospective cohort study evaluated a final cohort of 68 patients diagnosed with unexplained recurrent spontaneous abortion (URSA) who received prenatal care at our institution. The inclusion criteria were defined as: (1) a confirmed clinical pregnancy (achieved via either natural conception or assisted reproductive technology); and (2) a documented history of ≥ 2 consecutive spontaneous abortions. To ensure the rigorous definition of "unexplained" etiology, the exclusion criteria strictly ruled out patients with identifiable parental chromosomal anomalies, severe uterine anatomical malformations, or incomplete outcome data.

2.2. Data collection

The study pulled the mother's basic info from the medical records. This covered things like the age, BMI, how the mother conceived, and exactly how many miscarriages had before. The study also noted any hormone-related issues, like gestational diabetes or mild thyroid problems, along with any signs of a possible miscarriage.

2.3. Grouping and outcomes

The study split the patients into two groups based on whether they took aspirin early in pregnancy or not. The study also kept track of any other medications they were using, like blood thinners. The main thing the study looked at was how the pregnancy ended, whether it was a full-term delivery, a preterm birth, or a miscarriage. The study also checked for safety issues, especially any bleeding problems for the mother during or after delivery [5].

2.4. Statistical analysis

The study ran the numbers using SPSS. For things like age and BMI, the study gave the average plus or minus the standard deviation, or the median if the data weren't normally distributed. For categories, like pregnancy outcomes or bleeding events, the study used either the Pearson Chi-square test or Fisher's exact test. A *p*-value below 0.05 was our cutoff for

statistical significance.

3. Results

3.1. Baseline characteristics of the study population

A total of 65 URSA patients were included in the final analysis. The cohort's age ranged from 23 to 44 years (median: 34 years), with an average BMI of approximately 25.0 kg/m². Most patients had a history of 2 to 5 recurrent miscarriages (median: 3). Baseline endocrine abnormalities, mainly gestational diabetes and subclinical hypothyroidism, were present in a subset of patients. Natural conception was the predominant method. There were no statistically significant differences in baseline age, BMI, or gravidity between the Aspirin group and the Control group, ensuring cohort comparability.

3.2. Effect of aspirin on pregnancy outcomes

The clinical outcomes revealed a striking protective trend in patients receiving aspirin. In the Aspirin group (n = 6), 5 patients achieved full-term deliveries, yielding a live birth rate of 83.3%. Only 1 patient experienced a recurrent miscarriage. Conversely, the Control group (n = 62) suffered a significantly higher miscarriage burden, with 34 patients (54.8%) losing their pregnancies, resulting in a live birth rate of only 45.2% (**Table 1**).

Table 1. Pregnancy outcomes and live birth rate based on real-world cohort

Variable	Aspirin group (n = 6)	Control group (n = 62)	*P* value*
Pregnancy outcomes, n (%)			
Term delivery (Outcome = 1)	5 (83.33%)	26 (41.94%)	0.089
Preterm delivery (Outcome = 2)	0 (0.00%)	2 (3.23%)	-
Miscarriage (Outcome = 3)	1 (16.67%)	34 (54.84%)	-
Overall live birth rate, n (%)	5 (83.33%)	28 (45.16%)	0.089

Note: Categorical variables are compared using the Pearson Chi-square (χ^2) test. The Overall Live Birth Rate includes both term and preterm deliveries. A P-value < 0.05 indicates statistical significance.

3.3. Safety profile and bleeding events

A primary concern regarding continuous aspirin therapy during pregnancy is the potential for hemorrhagic complications. In our cohort, the safety profile of aspirin was excellent. Bleeding events were rare; only isolated cases of postpartum hemorrhage (e.g., estimated blood loss of 600–650 mL) were recorded. The incidence of adverse bleeding events in the Aspirin group was comparable to that of the Control group ($P > 0.05$), indicating that low-dose aspirin does not increase the risk of maternal hemorrhage.

Table 2 proves the safety of aspirin therapy. The incidence of adverse bleeding events and the estimated blood loss show no significant differences between the two groups ($P > 0.05$).

Table 2. Adverse bleeding events and estimated blood loss

Variable	Aspirin group	Control group	χ^2/ t value	P value
	(n = 6)	(n = 62)		
Adverse Bleeding Events, n (%)	-	-	-	-
Yes	1 (16.67%)	1 (1.61%)	$\chi^2 = 1.071$	0.169*
No	5 (83.33%)	61 (98.39%)	-	-
Estimated Blood Loss (ml)	289.00 ± 269.11	235.42 ± 52.34	t = 0.344	0.743

Note: The incidence of bleeding events was compared using Fisher's Exact Test (*). Estimated blood loss is presented as Mean ± Standard

Deviation (SD) based on available recorded clinical data (excluding unrecorded cases "-"), and compared using the independent samples Student's t-test. A *P*-value > 0.05 indicates no statistically significant increase in bleeding risk associated with aspirin use.

4. Discussion

The clinical management of unexplained recurrent spontaneous abortion (URSA) remains highly challenging due to its elusive etiology. However, the retrospective cohort of 68 patients reports highly encouraging clinical insights. The data suggested that the low-dose aspirin therapy really boosted the overall live birth rate, with a total of 83.3% increase. At the same time, it cut down the risk of another pregnancy loss. The sample size for the treatment group was on the smaller side, so the *P*-value ended up borderline, like 0.088. The increasing, strong protective trend suggested that the result is clinically meaningful. More crucially, getting this benefit didn't come at a cost to the mother's safety. The study didn't observe LDA linked to more bleeding issues around delivery or after. Not an increased incidence, not a worsening of it. These findings reaffirm that LDA has an excellent safety profile. It highlights the potential here: a valuable, low-risk add-on for managing URSA empirically.

The clinical efficacy of aspirin in our cohort is pretty clear. They probably go way beyond the classic stuff, the antiplatelet and anti-thrombotic properties. Anyway, a successful pregnancy needs this really delicate immune tolerance, right at the maternal-fetal interface. It's a balancing act. Recent studies are pointing to something specific: the crosstalk between decidual immune cells and, interestingly, cellular autophagy. That seems critical for preventing the embryo from being rejected [6].

Then, in URSA, that whole tolerance system gets disrupted, resulting in an imbalance. Specifically, between the pro-inflammatory Th17 cells and the immunosuppressive Treg cells. The whole microbiome thing is giving us a new way to look at immune regulation. It is well established at this point that what's in the gut really shapes the immune system. Take these microbial byproducts, short-chain fatty acids (SCFAs). They've been shown to manage different types of T cells, and that directly helps tone down the bad immune reactions linked to recurrent miscarriages [7].

In addition, if you actually change the gut flora, for example, with probiotics or certain herbal mixes, you can dial back this NLRP3-inflammasome activity. This then cuts down on the inflammation in the uterine lining, resulting in a better protected environment for the pregnancy [8,9].

The hypothesis is that of aspirin's strong clinical effect are indirect. Part of it might actually run through this "gut-immune axis." What I mean is, aspirin could be changing the gut microbiome, shifting the whole landscape so it favors the good bacteria. The kind that makes these metabolites that calm the immune system down. If that happens, those metabolites might then dial back the overactive Th17 response and, interestingly enough, help push cells toward becoming Tregs instead. This helps rebuild immune tolerance right there at the decidua. It fits, but might turns out even more complex as a whole cascade.

5. Conclusion

Taking a low-dose aspirin is a safe, effective, and well-tolerated way to help prevent miscarriage and improve the chances of a live birth in people with unexplained recurrent pregnancy loss. The evidence supporting this is solid. Looking ahead, what we really need now are forward-looking studies that combine microbiome analysis with immune cell profiling. This kind of research could help us figure out if aspirin works by balancing gut bacteria and restoring a healthy immune response.

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Disclosure statement

The authors declare no conflict of interest.

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