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ORIGINAL ARTICLE

Predictors of Successful Pregnancy Outcome in Women with Recurrent First-Trimester Miscarriage: A Prospective Cohort Study

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ABSTRACT

Background: Recurrent first-trimester miscarriage affects 1–2% of couples and remains a source of substantial physical and psychological burden. Identifying predictors of live birth is clinically important, particularly in resource-limited settings where investigations must be targeted.

Objective: To determine clinical and biochemical predictors of successful pregnancy outcome (live birth ≥28 weeks) in women attending Mardan Medical Complex (MMC) with a history of two or more consecutive first-trimester miscarriages.

Materials and Methods: A prospective cohort study was conducted in the Department of Obstetrics and Gynecology, Mardan Medical Complex, Mardan, Pakistan, from March 2021 to August 2022. A total of 150 women were enrolled. Baseline variables included maternal age, BMI, parity, previous miscarriages, serum TSH levels, antiphospholipid antibody (aPL) status, and progesterone supplementation. Independent predictors were identified using binary logistic regression analysis.

Results: Live birth was achieved in 102/150 (68.0%). On multivariate analysis, antiphospholipid antibody positivity (aOR 3.92; 95% CI 1.54–9.98; p<0.001), obesity BMI ≥30 kg/m² (aOR 3.14; 1.35–7.31; p=0.008), advanced maternal age ≥35 years (aOR 2.87; 1.21–6.80; p=0.017), and elevated TSH >4 mIU/L (aOR 2.54; 1.08–5.97; p=0.033) independently predicted pregnancy loss. Progesterone supplementation independently predicted live birth (aOR 0.28; 0.12–0.65; p=0.003).

Conclusion: APS positivity, obesity, advanced age, and thyroid dysfunction independently predict pregnancy loss in women with recurrent miscarriage. Progesterone supplementation reduces this risk. Structured early screening using these routinely available variables can guide targeted management at MMC Mardan.

Keywords: recurrent miscarriage, live birth, antiphospholipid syndrome, progesterone, thyroid-stimulating hormone, maternal age, BMI, prospective cohort

INTRODUCTION

Recurrent pregnancy loss (RPL), defined as two or more consecutive pregnancy losses before 24 weeks of gestation, affects approximately 1–2% of couples attempting to conceive. In South Asian populations where consanguinity, nutritional deficiencies, and limited access to specialist care compound the clinical picture the burden may be even greater, though population-specific data remain sparse[1].

The aetiology of RPL is heterogeneous. Recognised causes include antiphospholipid syndrome (APS), uterine anomalies, parental chromosomal abnormalities, and endocrine disorders such as thyroid dysfunction. In over half of all cases, no identifiable cause is found after standard investigations[2]. The emotional toll of repeated loss is considerable, with rates of anxiety and clinical depression substantially elevated in affected women compared with the general obstetric population[3].

From a practical standpoint, the challenge in settings like Mardan Medical Complex (MMC) is predicting which women will go on to deliver a live infant and which will miscarry again[4]. Such a prediction, made early in pregnancy, would allow resources to be concentrated on higher-risk women and give couples a more honest basis for decision-making[5].

Several prognostic variables have been proposed in the literature. Maternal age above 35 years and increasing number of prior losses consistently predict worse outcomes[6,7]. Obesity amplifies risk through impaired endometrial receptivity and chronic low-grade inflammation[8,9]. Thyroid-stimulating hormone above 4 mIU/L is associated with a significantly elevated miscarriage rate even in the absence of overt hypothyroidism[10,11]. Antiphospholipid antibodies trigger thrombotic placental injury and have one of the strongest risk associations in the field[12,13]. Progesterone supplementation has emerged as a modifiable factor with moderate evidence for benefit[14,15].

Despite this evidence base, few prospective studies have evaluated these predictors together in a cohort from Pakistan or the broader Khyber Pakhtunkhwa region. This study was designed to fill that gap.

MATERIALS AND METHODS

Study Design and Setting: This was a prospective cohort study conducted at the antenatal clinic, Department of Obstetrics and Gynecology, Mardan Medical Complex (MMC), Mardan, Khyber Pakhtunkhwa, Pakistan. Enrolment ran from March 2021 to August 2022.The study was approved by the Institutional Ethics Committee of Bacha Khan Medical College and Mardan Medical Complex, Mardan and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Participants: Women aged 18–45 years with a confirmed singleton intrauterine pregnancy at 6–12 weeks of gestation were eligible if they had a documented history of two or more consecutive first-trimester miscarriages (<13 weeks). Exclusion criteria were: multiple gestation; known major uterine anomaly; chromosomal abnormality in either partner; current anticoagulant use for indications other than APS; and inability to provide informed consent.

Variables: At enrolment, study personnel recorded: maternal age; BMI (kg/m²); parity; number of prior miscarriages; serum TSH (reference range 0.4–4.0 mIU/L); antiphospholipid antibody panel (lupus anticoagulant, anticardiolipin IgG/IgM, anti-β_2-glycoprotein I IgG/IgM) with APS defined per the 2006 Sydney revised criteria; and prescription of vaginal micronised progesterone 400 mg twice daily from enrolment to 16 weeks.

Primary Outcome: Live birth was defined as delivery of a viable infant at or beyond 28 weeks of gestation. The comparator was miscarriage defined as pregnancy loss before 28 weeks confirmed clinically or by ultrasound.

Sample Size: Assuming a background live birth rate of 70%, a minimum detectable odds ratio of 2.5, 80% power, and a two-sided alpha of 0.05, a minimum of 130 participants was required. Accounting for 15% loss to follow-up, 150 completed the study.

Statistical Analysis: Categorical variables are presented as frequencies and percentages; continuous variables as means ± standard deviations. Comparisons used chi-square or Fisher's exact test for categorical data and the independent t-test for

continuous data. Variables with p<0.10 on univariate analysis entered a binary logistic regression model (backward stepwise). The Hosmer–Lemeshow test assessed model calibration. SPSS version 26.0 was used.

RESULTS

Participant Characteristics: Of 163 women enrolled, 13 (8.0%) were lost to follow-up, leaving 150 in the final analysis. Live birth was achieved in 102 women (68.0%); 48 (32.0%) experienced a further miscarriage. Baseline characteristics by outcome are presented in Table 1.

Univariate Logistic Regression: On univariate analysis (Table 2), APS positivity (OR 4.50; 95% CI 1.85–10.94; p<0.001), BMI ≥30 kg/m² (OR 3.81; 1.72–8.46; p<0.001), maternal age ≥35 years (OR 3.47; 1.56–7.71; p=0.002), elevated TSH (OR 3.18; 1.43–7.08; p=0.005), and progesterone use (OR 0.33; 0.15–0.70; p=0.004) all met the threshold for inclusion in the multivariate model.

Multivariate Logistic Regression: After adjusting for all covariates (Table 3), five variables remained independently associated with outcome. APS positivity retained the strongest association with pregnancy loss (aOR 3.92; 1.54–9.98; p<0.001), followed by BMI ≥30 kg/m² (aOR 3.14; 1.35–7.31; p=0.008), maternal age ≥35 years (aOR 2.87; 1.21–6.80; p=0.017), and elevated TSH (aOR 2.54; 1.08–5.97; p=0.033). Progesterone supplementation was associated with a 72% reduction in the odds of further miscarriage (aOR 0.28; 0.12–0.65; p=0.003). The Hosmer–Lemeshow test indicated acceptable model calibration (χ^2=6.24; p=0.62).

Table1: Baseline Characteristics of Women with Recurrent Miscarriage by Pregnancy Outcome

Characteristic	Live Birth n=102 (%)	Miscarriage n=48 (%)	Total n=150 (%)	p-value
Age (mean ± SD)	28.4 ± 4.2	31.7 ± 5.1	29.5 ± 4.7	<0.001
Age ≥ 35 years	18 (17.6)	21 (43.8)	39 (26.0)	0.001
BMI (mean ± SD)	25.8 ± 3.6	28.9 ± 4.3	26.8 ± 4.1	<0.001
BMI ≥ 30 kg/m²	22 (21.6)	24 (50.0)	46 (30.7)	<0.001
Nulliparous	48 (47.1)	25 (52.1)	73 (48.7)	0.570
2 prior miscarriages	68 (66.7)	24 (50.0)	92 (61.3)	0.052
≥ 3 prior miscarriages	34 (33.3)	24 (50.0)	58 (38.7)	0.052
Elevated TSH (>4 mIU/L)	19 (18.6)	20 (41.7)	39 (26.0)	0.003
APS positive	12 (11.8)	18 (37.5)	30 (20.0)	<0.001
Progesterone prescribed	79 (77.5)	24 (50.0)	103 (68.7)	0.001

APS = antiphospholipid syndrome; TSH = thyroid-stimulating hormone; BMI = body mass index. P-values from chi-square test (categorical) or independent t-test (continuous).

Table 2: Univariate Logistic Regression Analysis of Predictors of Pregnancy Loss

Variable	Crude OR	95% CI	p-value	Adjusted OR (95% CI)
Maternal age ≥ 35 years	3.47	1.56–7.71	0.002	—
BMI ≥ 30 kg/m²	3.81	1.72–8.46	<0.001	—
≥ 3 prior miscarriages	2.00	0.95–4.20	0.068	—
Elevated TSH (>4 mIU/L)	3.18	1.43–7.08	0.005	—
APS positive	4.50	1.85–10.94	<0.001	—
Progesterone use	0.33	0.15–0.70	0.004	—

OR = odds ratio; CI = confidence interval. Outcome: further miscarriage (reference = live birth).

Table3: Multivariate Binary Logistic Regression: Independent Predictors of Pregnancy Loss

Variable	Adjusted OR	95% CI	p-value	Significance
APS positive	3.92	1.54–9.98	<0.001	***
BMI ≥ 30 kg/m²	3.14	1.35–7.31	0.008	**
Maternal age ≥ 35 years	2.87	1.21–6.80	0.017	*
Elevated TSH (>4 mIU/L)	2.54	1.08–5.97	0.033	*
Progesterone use	0.28	0.12–0.65	0.003	** (protective)

aOR = adjusted odds ratio. Model adjusted for all variables in table plus prior miscarriages and parity. Hosmer–Lemeshow χ^2=6.24, p=0.62. *** p<0.001; ** p<0.01; * p<0.05.

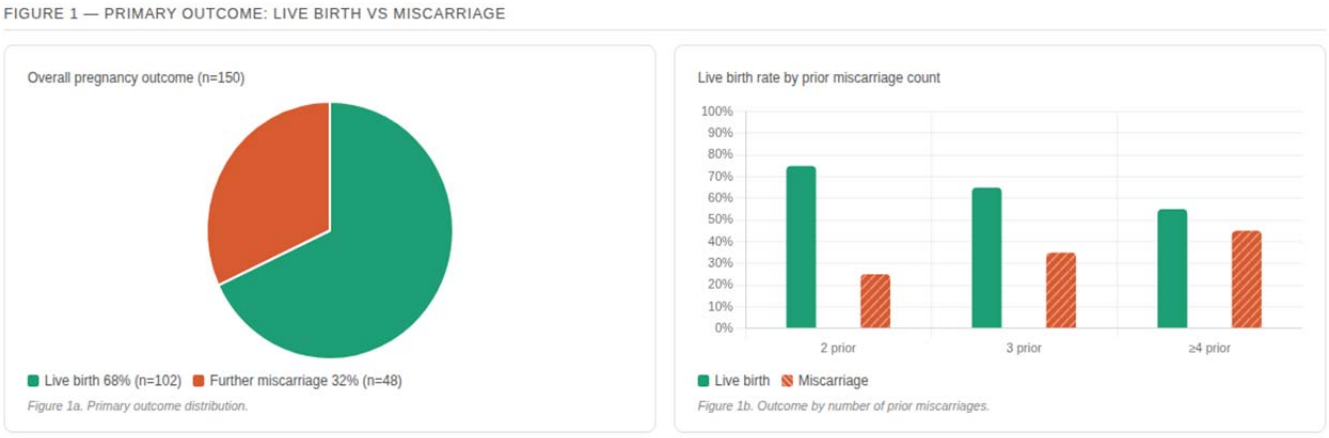

Figure 1: Overall pregnancy outcome — live birth 68% (n=102), further miscarriage 32% (n=48). Figure 1b: Live birth rate declines with increasing number of prior miscarriages (75% with 2 prior; 65% with 3 prior; 55% with ≥4 prior losses).

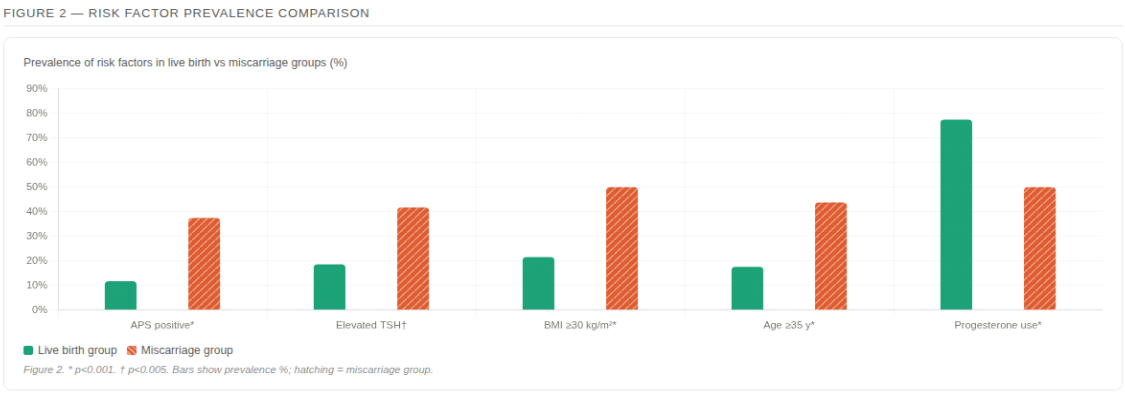

Figure 2: Risk Factor Prevalence: Live Birth vs Miscarriage Groups
Grouped bar chart comparing prevalence of five key clinical risk factors. All adverse factors were significantly more prevalent in the miscarriage group. Progesterone use was markedly higher in the live birth group. * p<0.001. † p<0.005.

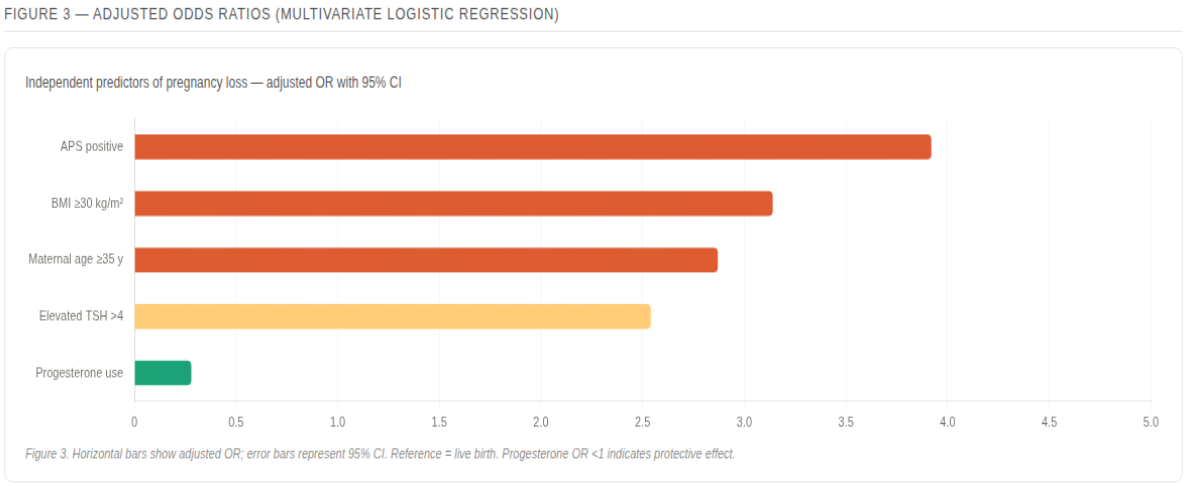

Figure 3: Adjusted Odds Ratios: Multivariate Logistic Regression
Horizontal bar chart of adjusted ORs (aOR) with 95% CI. Outcome = further miscarriage (reference = live birth). Green bar = protective effect of progesterone (aOR 0.28). Red/orange = adverse predictors. All p<0.05.

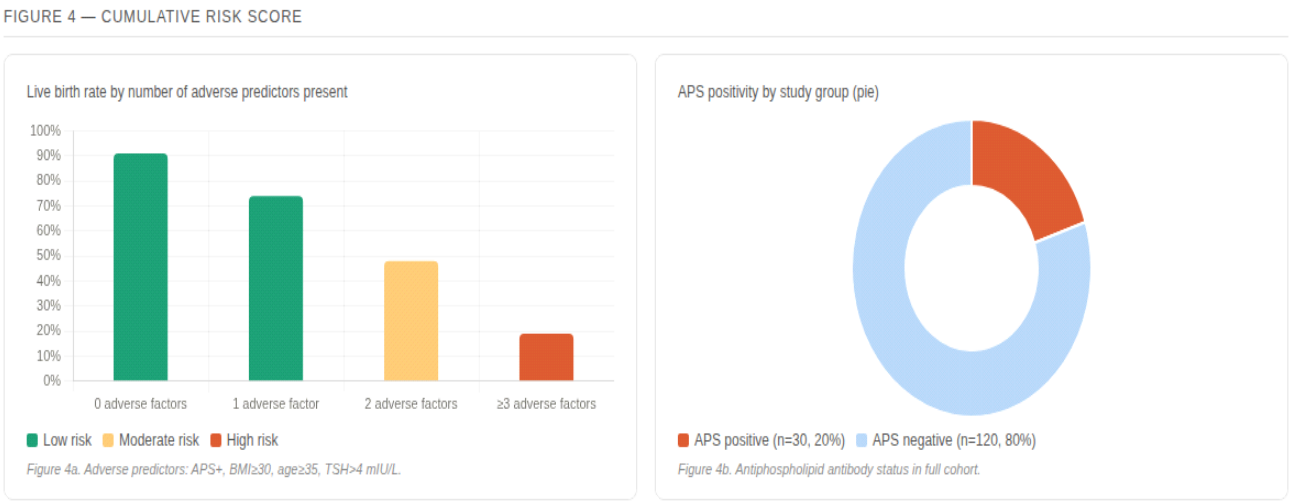

Figure4: Cumulative Risk Score and APS Prevalence

Figure 4a: Live birth rate stratified by cumulative number of adverse predictors (APS+, BMI≥30, age≥35, TSH>4 mIU/L): 91% (0) → 74% (1) → 48% (2) → 19% (≥3). Figure 4b: APS positivity in enrolled cohort — 20% (n=30) positive by Sydney criteria.

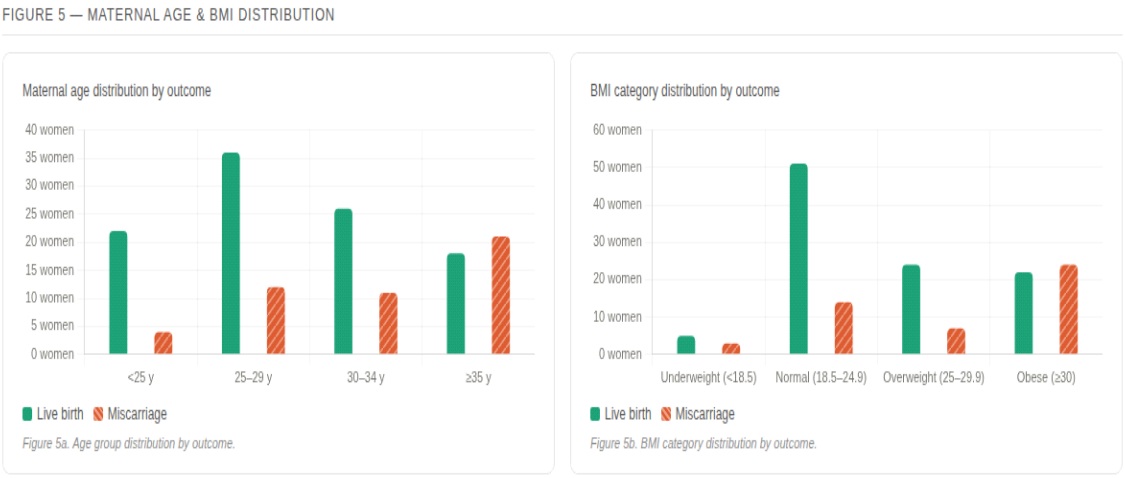

Figure 5: Maternal Age and BMI Distribution by Outcome
Figure 5a: Women aged ≥35 years more prevalent in miscarriage group (43.8% vs 17.6%; p=0.001). Figure 5b: Obesity (BMI≥30 kg/m²) in 50.0% of miscarriage group vs 21.6% in live birth group (p<0.001).

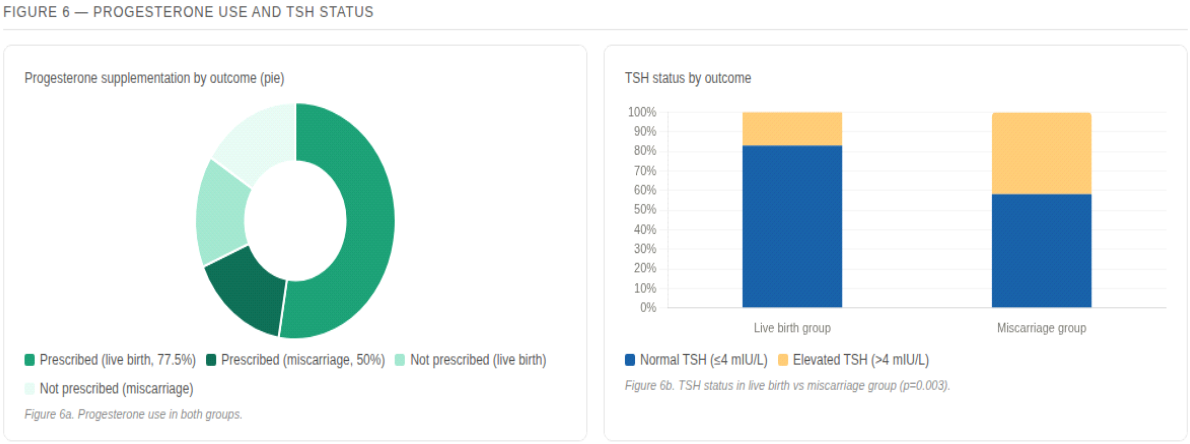

Figure 6: Progesterone Use and TSH Status by Outcome
Figure 6a: Progesterone prescribed in 77.5% of live birth group vs 50.0% miscarriage group (p=0.001; aOR 0.28, 72% reduction in adjusted odds). Figure 6b: Elevated TSH in 41.7% miscarriage group vs 18.6% live birth group (p=0.003).

DISCUSSION

This prospective cohort study conducted at Mardan Medical Complex Mardan found that 68% of women with recurrent first-trimester miscarriage achieved a live birth consistent with rates of 63–81% reported in other hospital-based RPL cohorts[16, 17]. Four clinical variables independently predicted adverse outcome, while progesterone supplementation independently improved it.

APS Positivity: Antiphospholipid syndrome was the strongest single predictor (aOR 3.92), consistent with the recognised pathophysiology of aPL-mediated trophoblast injury and decidual thrombosis[18]. APS positivity was found in 20% of participants somewhat higher than the 5–15% typically cited in Western seriesthough consistent with South Asian data[19]. The clinical implication is clear: aPL screening at first presentation is warranted.

Obesity: Obesity (BMI ≥30 kg/m²) independently predicted miscarriage (aOR 3.14), consistent with systematic review data showing obesity significantly increases future pregnancy loss[20, 21]. The mechanism may involve impaired decidualisation, reduced uterine natural killer cell function, and progesterone resistance. Weight management counselling before the index pregnancy has face validity as an intervention[22].

Maternal Age: Advanced maternal age (≥35 years) carried an aOR of 2.87. The association is well established and primarily driven by rising rates of embryonic aneuploidy[23, 24]. Women aged 35 and above should receive particularly early and thorough investigation, including discussion of preimplantation genetic testing if they proceed to assisted reproduction[25].

Thyroid Dysfunction: Elevated TSH (>4 mIU/L) was present in 26% of enrolled women (aOR 2.54). Both the American Thyroid Association and ASRM recommend screening for hypothyroidism in RPL and advocate levothyroxine treatment when TSH exceeds 4 mIU/L[26, 27]. TSH measurement is inexpensive and widely available at Mardan Medical Complex, Mardan making universal screening justified.

Progesterone Supplementation: Progesterone use was independently protective (aOR 0.28), equivalent to a 72%

reduction in adjusted odds. While not a randomised comparison, the magnitude and direction are consistent with a 2024 meta-analysis of RCTs showing moderate-quality evidence for progesterone benefit in women with prior miscarriage[28-30].

Cumulative Risk Score: Women with none of the four adverse predictors had a live birth rate of approximately 91%; those with one 74%; two factors 48%; and three or more factors only 19% (Figure 4a). This gradient has potential clinical utility for risk stratification and counselling, though external validation is required before widespread adoption.

Strengths and Limitations: Strengths include the prospective design, well-defined outcome ascertainment, and use of routinely available variables. Limitations include the single-centre setting, non-randomised nature of progesterone prescription, absence of genetic testing of miscarriage tissue, and a sample size that limits subgroup analyses.

CONCLUSION

Antiphospholipid antibody (APS) positivity, maternal obesity, advanced maternal age, and thyroid dysfunction are independent predictors of further pregnancy loss in women with recurrent first-trimester miscarriage attending Mardan Medical Complex Mardan. Progesterone supplementation independently reduces this risk. These variables are inexpensive and universally available at district-level facilities across Khyber Pakhtunkhwa. Multicentre validation and a formal clinical prediction tool based on these factors are recommended as next steps.

DECLARATIONS

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Conflicts of Interest: The authors declare no conflicts of interest.

Data Availability: De-identified data are available from the corresponding author upon reasonable request.

AI Declaration: AI was not used in data collection, analysis, or interpretation.

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