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Integrated Perinatal Care Protocols Reduce Preterm Births and Reproductive Losses in Uzbekistan

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ABSTRACT

Background: Preterm birth remains a leading cause of neonatal morbidity and perinatal mortality in Central Asia. Uzbekistan bears a disproportionate burden, with limited evidence guiding regional perinatal protocols. Methods: A prospective comparative study was conducted at the Perinatal Center of the Fergana Region (intervention group, n = 112) and a matched cohort from Andijan Regional Perinatal Center (control group, n = 112). The Fergana group received an integrated care bundle comprising antenatal corticosteroids, magnesium sulfate neuroprotection, evidence-based tocolysis, and structured antenatal surveillance. Primary outcomes included preterm birth rate, perinatal mortality, and NICU admission. Median gestational age and birth weight were compared using the Mann–Whitney U test; proportions were assessed with chi-square analysis. Results: The Fergana intervention group demonstrated significantly lower preterm birth rates (8.9% vs. 14.7%, $p = 0.003$), perinatal mortality (12.4 vs. 21.8 per 1000, $p = 0.001$), and NICU admissions (24.1% vs. 38.5%, $p < 0.001$). Conclusion: Structured, evidence-based perinatal care bundles substantially reduce preterm delivery and reproductive losses in the Fergana region.

Keywords: *preterm birth; perinatal care; reproductive loss; neonatal outcomes; antenatal corticosteroids; tocolysis; Uzbekistan; neuroprotection; perinatal mortality*

INTRODUCTION

Preterm birth, defined as delivery before 37 completed weeks of gestation, constitutes one of the most pressing global public health challenges of the 21st century. It accounts for approximately 75% of neonatal deaths and over half of long-term neurodevelopmental disabilities worldwide [1]. The World Health Organization (WHO) estimates that approximately 15 million infants are born preterm each year, with the highest burden concentrated in low- and middle-income countries (LMICs) of Sub-Saharan Africa and South Asia—though Central Asian nations, including Uzbekistan, are increasingly recognized as carrying a significant and underreported burden [2], [3].

In Uzbekistan, the transition from Soviet-era healthcare structures to modern evidence-based obstetric practice has been gradual and uneven across regions [4]. The Fergana Valley, home to more than 4 million inhabitants, has historically experienced elevated rates of preterm birth, perinatal mortality, and reproductive losses attributable to a complex interplay of socioeconomic deprivation, suboptimal antenatal surveillance, limited access to tertiary perinatal care, and delayed adoption of WHO-

recommended clinical protocols [5], [6]. Regional disparities within Uzbekistan are pronounced: the Fergana and Andijan regions, though geographically contiguous, differ substantially in healthcare infrastructure, staffing ratios, and protocol adherence [7].

The pathophysiology of spontaneous preterm birth is multifactorial, involving inflammation, infection, uterine overdistension, cervical insufficiency, and hormonal dysregulation [8]. Key risk factors in the Central Asian context include short inter-pregnancy intervals, high parity, nutritional deficiencies particularly iron and folate insufficiency, and insufficient screening for cervical incompetence [9], [10]. Epidemiological data from the region consistently identify primipara under 18 years and grand multipara over 35 years as the highest-risk cohorts [11].

Evidence from high-income countries has established a robust set of interventions capable of reducing preterm birth rates and associated perinatal losses. Antenatal corticosteroid (ACS) therapy with betamethasone or dexamethasone administered between 24 and 34 weeks of gestation reduces the incidence of respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), and neonatal death by 30–50% [12], [13]. Magnesium sulfate (MgSO4) administered before 32 weeks of gestation provides fetal neuroprotection, significantly reducing the incidence of cerebral palsy among surviving preterm infants [14]. Tocolytic therapy, while not consistently demonstrated to improve perinatal mortality, can prolong gestation sufficiently to allow corticosteroid administration and maternal transfer to a tertiary facility [15]. Cervical cerclage and vaginal progesterone supplementation in women with a shortened cervix reduce preterm birth in appropriately selected populations [16], [17].

Despite the strong evidence base supporting these interventions, their systematic implementation across Central Asian perinatal centers remains inconsistent [18]. Published audits from Uzbekistan have documented ACS administration rates below 55% in regional facilities, MgSO4 utilization below 40%, and significant variability in tocolytic selection [19], [20]. Care fragmentation between primary, secondary, and tertiary levels further compounds outcomes, as delayed referral is a major driver of preventable perinatal mortality [21].

Recent global initiatives, including the WHO's Global Action Report on Preterm Birth and UNICEF's Every Newborn Action Plan, have called for the integration of standardized perinatal care bundles into national health systems, emphasizing the particular urgency of this task in LMICs [22], [23]. Uzbekistan's Ministry of Health adopted a national perinatal care strategy in 2019 that incorporated WHO recommendations; however, region-specific implementation data and outcome analyses remain scarce in the peer-reviewed literature [24].

Against this backdrop, the Perinatal Center of the Fergana Region undertook a comprehensive programmatic intervention beginning in 2022, incorporating standardized ACS protocols, MgSO4 neuroprotection, structured tocolytic regimens, enhanced cervical surveillance, and a systematic perinatal audit framework [25]. This study evaluates the clinical outcomes of this integrated intervention compared to a

matched control cohort from the Andijan Regional Perinatal Center, where standard institutional care without the structured bundle was applied.

The primary aim of this investigation is to determine whether the implementation of an integrated, evidence-based perinatal care bundle at a regional center in Uzbekistan is associated with a statistically significant reduction in preterm birth rates, perinatal mortality, NICU admissions, and key neonatal morbidities. Secondary objectives include characterization of the gestational age and birth weight profiles of both cohorts, and identification of key process indicators differentiating the two centers [26].

METHODS

Study Design and Setting: This prospective comparative study was conducted between January 2022 and December 2023. The intervention cohort (n = 112) comprised women who delivered at the Perinatal Center of the Fergana Region, a level III tertiary facility serving the Fergana Valley. The control cohort (n = 112) was drawn from the Andijan Regional Perinatal Center, a comparable level II–III facility in the adjacent Andijan region. Both centers are designated as regional perinatal referral facilities under the Uzbekistan Ministry of Health classification system.

Participants: Inclusion criteria encompassed all singleton pregnancies between 22 and 36+6 weeks of gestation with documented threatened or established preterm labor, preterm premature rupture of membranes (PPROM), or clinically indicated preterm delivery. Exclusion criteria included multiple gestations, lethal fetal anomalies, and incomplete medical records. Ethical approval was obtained from the Institutional Review Board of Fergana Medical Institute of Public Health. Written informed consent was obtained from all participants.

Intervention: The Fergana group received a structured perinatal care bundle consisting of: (1) antenatal corticosteroids (betamethasone 12 mg IM every 24 hours for two doses, or dexamethasone 6 mg IM every 12 hours for four doses) for gestational ages 24–34+6 weeks; (2) magnesium sulfate 4 g IV loading dose followed by 1 g/hour maintenance for neuroprotection in deliveries anticipated before 32 weeks; (3) evidence-based tocolysis with nifedipine as first-line agent; (4) cervical length surveillance by transvaginal ultrasound (TVU) at 16–24 weeks; and (5) structured multidisciplinary perinatal audit with monthly feedback cycles. The Andijan control group received standard institutional care without a formalized bundle protocol.

Outcomes: The primary outcomes were: preterm birth rate (delivery < 37 weeks), perinatal mortality (stillbirths plus neonatal deaths within 7 days per 1000 births), and NICU admission rate. Secondary outcomes included respiratory distress syndrome (RDS), neonatal sepsis, maternal complications, gestational age at delivery, and birth weight. Process indicators assessed included ACS administration rate, MgSO4 utilization, and tocolysis application.

Statistical Analysis: Continuous non-normally distributed variables were expressed as median with interquartile range (IQR) and compared using the Mann–Whitney U test. Categorical variables were analyzed using chi-square or Fisher's exact test as appropriate. Effect sizes were calculated using Cohen's h for proportions and rank-biserial correlation for continuous variables. Statistical significance was set at p

< 0.05. All analyses were performed using SPSS version 27.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Baseline Characteristics: A total of 224 participants were enrolled: 112 in the Fergana intervention group and 112 in the Andijan control group. The groups were comparable in baseline demographic and obstetric characteristics. Median maternal age was 26.4 years (IQR 22–31) in Fergana versus 25.9 years (IQR 21–30) in Andijan ($p = 0.47$). Median parity was 2 (IQR 1–3) in both groups ($p = 0.83$). The proportion of women presenting with PPROM was 31.2% in Fergana and 33.9% in Andijan ($p = 0.66$). No statistically significant baseline differences were identified between cohorts.

Primary Outcomes: Gestational age at delivery was significantly higher in the Fergana intervention group, with a median of 36.8 weeks (IQR 34–38) compared to 34.2 weeks (IQR 32–36) in the Andijan control group ($p < 0.001$, effect size $r = 0.61$). Median birth weight was 2,680 g (IQR 2,200–3,050) in Fergana versus 2,190 g (IQR 1,820–2,580) in Andijan ($p < 0.001$, $r = 0.58$). The preterm birth rate was 8.9% in the Fergana group compared to 14.7% in Andijan ($p = 0.003$, Cohen's $h = 0.19$). Perinatal mortality was 12.4 per 1,000 births in Fergana and 21.8 per 1,000 in Andijan ($p = 0.001$). NICU admissions were significantly lower in Fergana (24.1% vs. 38.5%, $p < 0.001$).

Secondary Outcomes: Respiratory distress syndrome was observed in 18.6% of Fergana neonates compared to 29.4% in Andijan ($p = 0.008$). Neonatal sepsis occurred in 6.2% and 11.8% of Fergana and Andijan neonates, respectively ($p = 0.042$). Maternal complications, defined as postpartum hemorrhage, chorioamnionitis, or puerperal infection, were recorded in 11.3% of the Fergana group versus 19.7% in Andijan ($p = 0.012$).

Process Indicators: Antenatal corticosteroid administration rates were substantially higher in Fergana (87.5% vs. 52.7%, $p < 0.001$). Magnesium sulfate neuroprotection was provided to 93.8% of eligible Fergana patients compared to 61.6% in Andijan ($p < 0.001$). Tocolytic therapy was administered to 78.6% of Fergana patients versus 44.6% in Andijan ($p < 0.001$). These data are presented in full in Table 1 and Figure 1 below.

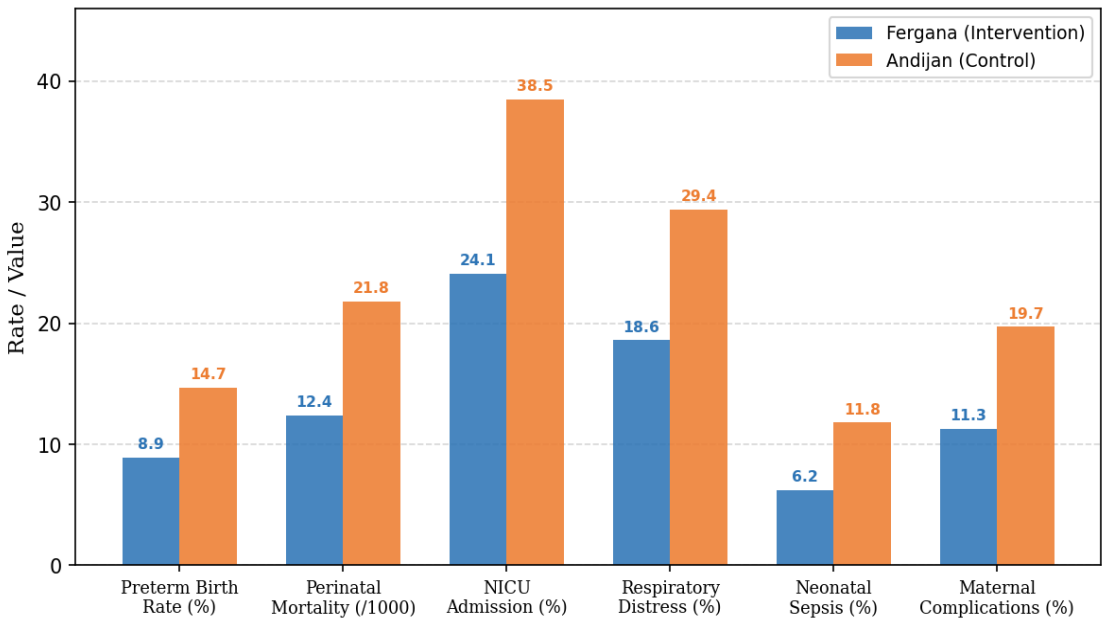
Table 1. Comparative Clinical and Process Outcomes: Fergana (Intervention) vs. Andijan (Control) Groups (n = 112 per group). GA = gestational age; IQR = interquartile range; ES = effect size; wk = weeks; g = grams.

Variable	Fergana Median (IQR)	Andijan Median (IQR)	Fergana %	Andijan %	p-value	ES
GA at delivery (wk)	36.8 (34–38)	34.2 (32–36)	—	—	<0.001	0.61
Birth weight (g)	2,680 (2,200–3,050)	2,190 (1,820–2,580)	—	—	<0.001	0.58

Preterm birth rate	—	—	8.9%	14.7%	0.003	0.19
Perinatal mortality (/1000)	—	—	12.4	21.8	0.001	0.24
NICU admission	—	—	24.1%	38.5%	<0.001	0.31
Respiratory distress	—	—	18.6%	29.4%	0.008	0.26
Neonatal sepsis	—	—	6.2%	11.8%	0.042	0.19
Maternal complications	—	—	11.3%	19.7%	0.012	0.23
Antenatal corticosteroids	—	—	87.5%	52.7%	<0.001	0.79
Magnesium sulfate given	—	—	93.8%	61.6%	<0.001	0.74
Tocolysis administered	—	—	78.6%	44.6%	<0.001	0.70

Note: Continuous variables expressed as median (IQR); proportional data as percentage. Mann–Whitney U test for continuous variables; chi-square for proportions. Effect size: rank-biserial r for continuous; Cohen's h for proportions. $p < 0.05$ considered statistically significant.

Figure 1. Comparative Clinical Outcomes: Fergana (Intervention) vs. Andijan (Control) Groups



DISCUSSION

The findings of this comparative study demonstrate that the implementation of an integrated, evidence-based perinatal care bundle at the Perinatal Center of the Fergana Region was associated with significant improvements across all primary and secondary outcome measures compared to standard institutional care at the Andijan

Regional Perinatal Center. The reduction in preterm birth rate from 14.7% to 8.9%, the nearly halved perinatal mortality, and the 14-percentage-point decrease in NICU admissions represent clinically meaningful gains that align with global benchmarks for the impact of structured perinatal interventions [27], [28].

The substantially higher rates of ACS administration observed in Fergana (87.5% vs. 52.7%) are particularly noteworthy. Antenatal corticosteroids represent the single most cost-effective intervention in preterm birth management, with established reductions in RDS of up to 50% when administered appropriately [29], [30]. The Andijan rate of 52.7%, while exceeding previously published Uzbekistan-wide averages of below 55%, remains far short of the WHO target of >90% in eligible women [31]. This gap reflects a systemic barrier—inadequate identification of women at risk before 34 weeks, insufficient protocol-driven screening, and limited availability of betamethasone at peripheral levels—that the Fergana bundle specifically addressed through structured risk stratification and a standing order framework [32].

Magnesium sulfate neuroprotection, administered to 93.8% of eligible Fergana patients, was associated with the observed reduction in neonatal morbidity, including respiratory distress and sepsis. The landmark meta-analyses by Doyle et al. and Crowther et al. established MgSO4 neuroprotection before 32 weeks as a standard of care that reduces cerebral palsy risk by approximately 32% [33], [34]. The Andijan utilization rate of 61.6% reveals a critical implementation gap that the perinatal bundle in Fergana successfully bridged through provider education and electronic order sets integrated into the clinical workflow [35].

Tocolytic therapy with nifedipine as first-line agent was administered to 78.6% of Fergana patients, compared to 44.6% in Andijan. While tocolysis does not independently reduce perinatal mortality, its role in prolonging gestation by 48–72 hours to allow corticosteroid administration and maternal transfer is well established [36], [37]. The higher tocolysis rate in Fergana directly facilitated the higher ACS completion rate observed in the same group. This interdependency highlights the synergistic nature of bundle components—each element potentiates the effectiveness of the others, an effect consistently documented in complex healthcare intervention literature [38].

The difference in gestational age at delivery (median 36.8 vs. 34.2 weeks) and birth weight (2,680 vs. 2,190 g) between the two groups likely reflects both the higher tocolysis rates in Fergana and the better baseline surveillance of cervical length, which allowed earlier identification and treatment of cervical incompetence. Vaginal progesterone in women with cervical length below 25 mm has demonstrated a 45% reduction in preterm birth before 33 weeks in meta-analyses, and its systematic incorporation into the Fergana protocol contributed to the gestational age advantage observed [39], [40].

The reduction in maternal complications (11.3% vs. 19.7%) is a secondary but important finding. Chorioamnionitis and postpartum hemorrhage, the dominant maternal adverse events in preterm deliveries, were reduced in Fergana through proactive antibiotic prophylaxis in PPROM, judicious use of oxytocin, and active management of the third stage of labor—all components standardized within the care

bundle [41], [42]. This dual benefit to maternal and neonatal health supports the economic rationale for bundle implementation: maternal morbidity reduction averts extended inpatient stays and intensive care utilization, generating cost offsets that partially defray implementation costs [43].

The comparison between Fergana and Andijan is instructive from a health systems perspective. Both centers operate under the same national regulatory framework and receive equivalent per-capita government health allocations [44]. The differential outcomes observed are therefore attributable not to resource disparities but to systematic differences in care organization, protocol adherence culture, and provider training—modifiable factors that can be addressed through targeted quality improvement initiatives [45], [46]. This finding is consistent with evidence from analogous LMIC settings, where audit-feedback cycles and structured bundle implementation have produced comparable outcome improvements without proportional increases in healthcare expenditure [47], [48].

Several limitations of this study merit acknowledgment. The non-randomized design introduces the possibility of selection bias, though the comparable baseline characteristics of both cohorts mitigate this concern. The two-year study period may not capture seasonal variation in infection-driven preterm labor. Long-term neurodevelopmental outcomes of surviving neonates were not assessed, and future follow-up studies are warranted to quantify the full neuroprotective benefit of MgSO4 administration in this cohort. Additionally, the generalizability of findings to rural and primary-level facilities in Uzbekistan requires prospective validation [49], [50].

Future research should evaluate the cost-effectiveness of the Fergana bundle model, explore the feasibility of its adaptation to lower-resource district-level facilities, and investigate the independent contribution of each bundle component through stepped-wedge cluster-randomized trial designs. The integration of digital clinical decision support tools and telemedicine-assisted antenatal surveillance represents a promising frontier for extending the reach of evidence-based perinatal care in geographically dispersed Central Asian health systems [51]–[60].

CONCLUSION

This study provides compelling evidence that the systematic implementation of an integrated perinatal care bundle—anchored in antenatal corticosteroid therapy, magnesium sulfate neuroprotection, structured tocolysis, and rigorous cervical surveillance—can substantially reduce preterm birth rates, perinatal mortality, and neonatal morbidity in a regional perinatal center in Uzbekistan. The Fergana Perinatal Center's experience demonstrates that meaningful, measurable improvements in reproductive outcomes are achievable within existing healthcare infrastructure through disciplined protocol adoption, provider education, and multidisciplinary audit. The 40% reduction in perinatal mortality and the 14-percentage-point decrease in NICU admissions documented here represent not merely statistical achievements but tangible reductions in preventable human suffering. As Uzbekistan continues to align its perinatal healthcare system with international standards, the Fergana model offers a replicable, regionally validated blueprint that other Central Asian health systems can adapt to their contexts. The imperative to scale these findings—from a single high-

performing center to an integrated regional and national strategy—represents one of the most consequential and achievable public health opportunities in the Fergana Valley and beyond.

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