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ROLE OF CLEXANE TO IMPROVE AFI AFTER 28 WEEKS GESTATION

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ABSTRACT

Objective:
Oligohydramnios is when the AFI is less than or equal to 5 cm. Borderline AFI ranges from 5.1 cm to 8 cm. Incidence of borderline AFI compared to normal AFI (8.1–18 cm) varies from 6% to 44% as mentioned in the studies. Decreased amniotic fluid can cause severe consequences to both mother and the fetus. This research analyzed the efficacy of Clexane in amniotic fluid index AFI levels among pregnant women following gestation

at 28 weeks or more, additional to standard treatment, and establishes risk factors that contribute both to AFI values and to neonate results.

Methods:

A randomized controlled trial (RCT) was conducted from January 2023 to June 2023 at a Divisional Headquarters Teaching Hospital Mirpur, Azad Kashmir. A total of 200 pregnant women at 28–34 weeks of gestation diagnosed with oligohydramnios (AFI <5 cm) were enrolled. Participants were randomly assigned into two groups: Group A received conventional treatment, including intravenous fluid, tablet Aspirin (150 mg daily), and rest in the lateral position, while Group B received Clexane (40 mg subcutaneously daily) in addition to the conventional treatment. AFI measurements were performed by radiologists using standard 4-quadrant measurements in the radiology department twice weekly after the initiation of treatment. Neonatal outcomes, including birth weight and the need for admission to neonatal intensive care units (NICU), were recorded. Statistical analyses, including Chi-squared and Fisher's Exact tests, were used to compare the efficacy of the treatments, and multivariate logistic regression was performed to adjust for potential confounding factors.

Results:

In this study, 200 patients had an improvement of AFI of 65% (n=130) within a period of 4 weeks. Group B, which received additional Clexane to their conventional treatment, showed more of a mean increase in AFI at 3.6 cm compared to group A at 1.7 cm, ($p<0.001$). Maternal obesity defined as BMI >30 was seen to have less improvement of AFI, $p=0.006$ and maternal hypertension. Newborns of mothers belonging to Group B had a higher mean birth weight, though, with $p=0.01$, but there were less NICU admissions for neonates born to the mothers belonging to Group A. No significant adverse effect occurred due to Clexane use.

Conclusions:

The addition of Clexane to the conventional treatment significantly improves the AFI in pregnant women with oligohydramnios after 28 weeks of gestation. It positively impacts neonatal outcomes such as higher birth weight and reduced NICU admissions. Maternal obesity and hypertension are identified as a risk factor that may make the efficacy of Clexane reduced. These studies suggest that Clexane can be a valuable therapy for the management of oligohydramnios and neonatal health improvement. The study suggests further research on long-term outcomes of the maternal and neonates.

KeyWords:

Clexane, Amniotic Fluid Index, Oligohydramnios, Preterm Birth, Neonatal Intensive Care Unit, Maternal Weight, Hypertension, Birth Weight, Cesarean Section.

INTRODUCTION

Amniotic fluid is important for fetal development, providing basic protection, nutrient exchange, and growth conditions [1]. AFI has become one of the most important parameters measured by ultrasound as an indicator of fetal well-being, especially in late gestation [2].

Low AFI, or oligohydramnios, is associated with several adverse perinatal outcomes: FGR, preterm birth, increased perinatal morbidity, and mortality [3,4]. A recent study on the prevalence of oligohydramnios noted that the condition was reported in 4.4% of pregnancies among 89,050 cases from China. The study places much emphasis on oligohydramnios as an important condition that presents with adverse perinatal outcomes, speaking to careful monitoring, especially in developing countries where consistent prenatal care is not readily available [5]. A related study on oligohydramnios conducted at a tertiary hospital in India reported that emergency lower segment cesarean sections (LSCS) were performed in 78% of the cases.

The most common idiopathic causes were noted, and routine ultrasound assessments led to earlier diagnosis. The results of this study establish a connection of oligohydramnios with severe perinatal complications. The findings of the research are reflective of the complexity of etiology and challenges in the management of the condition in South Asian settings [6]. According to Sultana et al, in Pakistan, in high-risk pregnancies, cases of post-dated delivery were 25%, 23% pregnancy-induced hypertension, 16% of them suffered from chronic hypertension, 14% intrauterine growth restriction, and 5% diabetes along with 17% other undiagnosed risks that could be due to either anemia, malnutrition, smoking, or a few other diseases. High-risk pregnancy often leads to low AFI [7]. Current interventions to enhance fetal movement in an AFI of less than 30 cm include antenatal hydration, bed rest, and in selected settings, amnioinfusion; however, these interventions often fail to provide effective and practical action [8,9].

Thus, studies towards pharmacologic interventions to enhance AFI have received increasing attention. LMWHs, among them Clexane or enoxaparin, have shown the potential use in obstetrics beyond being used as anti-thromboprophylactic agents. LMWHs possess anticoagulant and anti-inflammatory properties that enhance uteroplacental perfusion, thus enhancing the AFI levels by controlling uterine blood flow and placental function [10]. Some of the most recent research studies conducted indicate a possible promising approach to using LMWH for oligohydramnios, whereby LMWH stimulates angiogenesis in the placental vasculature to support the production of amniotic fluid in pregnancies at risk of fetal hypoxia and growth restriction [11,12]. Many international reports have pointed to a future role of Clexane in high-risk pregnancies. Jacobson observed that Clexane significantly reduces pregnancy loss in high-risk

pregnancies and the results are better compared to aspirin or no treatment. Thus, the study promotes the safety and efficacy of Clexane in such cases and AFI as well as birth outcomes may be indirectly improved, thereby pinpointing its promising role in obstetric care for at-risk pregnancies [13].

A European study concluded that therapies aimed at vascularity, with a regimen such as pentoxifylline plus vitamin E, resulted in an overall significant decrease in uterine artery resistance with increased indices of vascularity that correlated to enhanced pregnancy rates. In other words, not being primarily based on LMWH therapy, the report points toward potential therapy using enhancement of uterine artery flow with the consequent diminution in resistance for pregnancy [14].

Recently, a study in the Middle East has looked at how LMWH therapy influences first- and second-trimester screening test performance in thrombophilic pregnant women. The administration of LMWH alters MoM values for serum markers; this has implications for obstetricians in the management of such high-risk pregnancies [15]. The evidence thus presents the intervention with Clexane as being central to the management of oligohydramnios in any health setup.

Regionally, studies conducted in South Asia have also revealed the advantages of Clexane in improving AFI. In India, one study in which enoxaparin was administered in 86.32% of the cases specifically for females, 79.48% of which were prescriptions from the obstetrics and gynecology department. Consultants administered enoxaparin in 62.39% of the cases, where its effectiveness and safety are already established for patients at risk of preterm delivery [16].

Pakistani studies also endorse such findings by showing increased levels of AFI and neonatal outcomes among pregnant women in the third trimester who were administered Clexane. This is very significant especially for complicated hypertension [17]. In a country like Pakistan, prevalent practices do not include it in AFI management programs, although the recent assessments of institutes reveal that instituting it might be worthwhile to treat risky pregnancies adequately, particularly where conventional strategies are ineffective [18].

This study seeks to evaluate if Clexane is an effective agent in enhancing AFI among women who, at or after 28 weeks gestation, develop oligohydramnios in Pakistan. In an attempt to contribute to obstetric practices that are based on evidence and may, as such, reduce morbidity and mortality perinatal, this study investigates its role in the enhancement of AFI. This means better understanding the role of Clexane in reducing complicated cases related to low AFI in late gestations, thereby improving the well-being of the fetus-especially in areas with scarce delivery of high-level prenatal cares.

METHODS

This randomized controlled trial (RCT) was conducted from January 2023 to June 2023 at Divisional Headquarters Teaching Hospital Mirpur, Azad Kashmir, to evaluate the efficacy of Clexane (Enoxaparin) in enhancing the amniotic fluid index (AFI) in pregnant women diagnosed with oligohydramnios after 28 weeks of gestation.

A total of 200 pregnant women between 28 and 34 weeks of gestation, diagnosed with oligohydramnios (AFI < 5 cm), were enrolled. Participants were randomly assigned into two groups using a computer-generated random number sequence, and allocation was concealed using sealed opaque envelopes to avoid selection bias. Group A received conventional treatment, consisting of intravenous fluids, 150 mg daily Aspirin, and rest in the lateral position. Group B received Clexane (40 mg subcutaneously daily) in addition to the conventional treatment.

The sample size was calculated based on a power analysis to detect a statistically significant difference in AFI improvement between the two groups. Assuming an effect size of 0.5, a power of 80%, and an alpha level of 0.05, a minimum of 94 participants per group was required. To account for potential dropouts and ensure robust results, we increased the sample size to 100 participants per group, resulting in a total of 200 participants.

Inclusion criteria were singleton pregnancies between 28 and 34 weeks of gestation with an AFI < 5 cm. Exclusion criteria included multiple gestations, fetal congenital anomalies, known coagulation disorders, and pre-existing anticoagulant therapy. All participants provided informed consent prior to enrollment, and the study received ethical approval from the institutional review board.

The primary outcome was the change in AFI from baseline, which was assessed by certified radiologists using the standard 4-quadrant measurement technique. AFI measurements were performed twice weekly, and radiologists were blinded to group allocation. Secondary outcomes included neonatal birth weight and the need for admission to a neonatal intensive care unit (NICU), recorded at delivery.

Maternal characteristics, including age, BMI, parity, and a history of pre-existing conditions such as hypertension, were documented at enrollment. AFI improvement and neonatal outcomes were compared between the groups using independent t-tests for continuous variables and Chi-squared or Fisher's exact tests for categorical variables. A multivariate logistic regression model was used to adjust for confounding variables, such as maternal BMI and baseline AFI.

Data analysis was performed using statistical software. Continuous outcomes (e.g., AFI, birth weight) were analyzed using independent t-tests, while categorical outcomes (e.g., NICU admissions) were assessed using Chi-squared or Fisher's exact tests. Multivariate logistic regression was applied to adjust for potential confounders, including maternal BMI and baseline AFI. The statistical significance threshold was set at $p < 0.05$. An intention-to-treat analysis was conducted to include all randomized participants in the final analysis, regardless of study completion or loss to follow-up.

Throughout the trial, safety monitoring was conducted to track adverse effects, including bleeding or allergic reactions related to Clexane. No significant adverse effects were reported, and any minor events were promptly addressed. The study adhered to ethical guidelines, maintaining participant confidentiality with the use of unique identification numbers.

RESULTS

After four weeks of treatment, the outcomes for pregnant women with oligohydramnios (AFI <5 cm) were analyzed across two treatment groups: conventional therapy alone (Group A) and conventional therapy combined with Clexane (Group B). The primary outcomes of AFI improvement, neonatal birth weight, and NICU admissions were evaluated in both groups, with additional considerations for demographic factors, particularly maternal BMI and hypertension. The results revealed significant differences in AFI improvement, neonatal outcomes, and the influence of maternal factors on treatment efficacy.

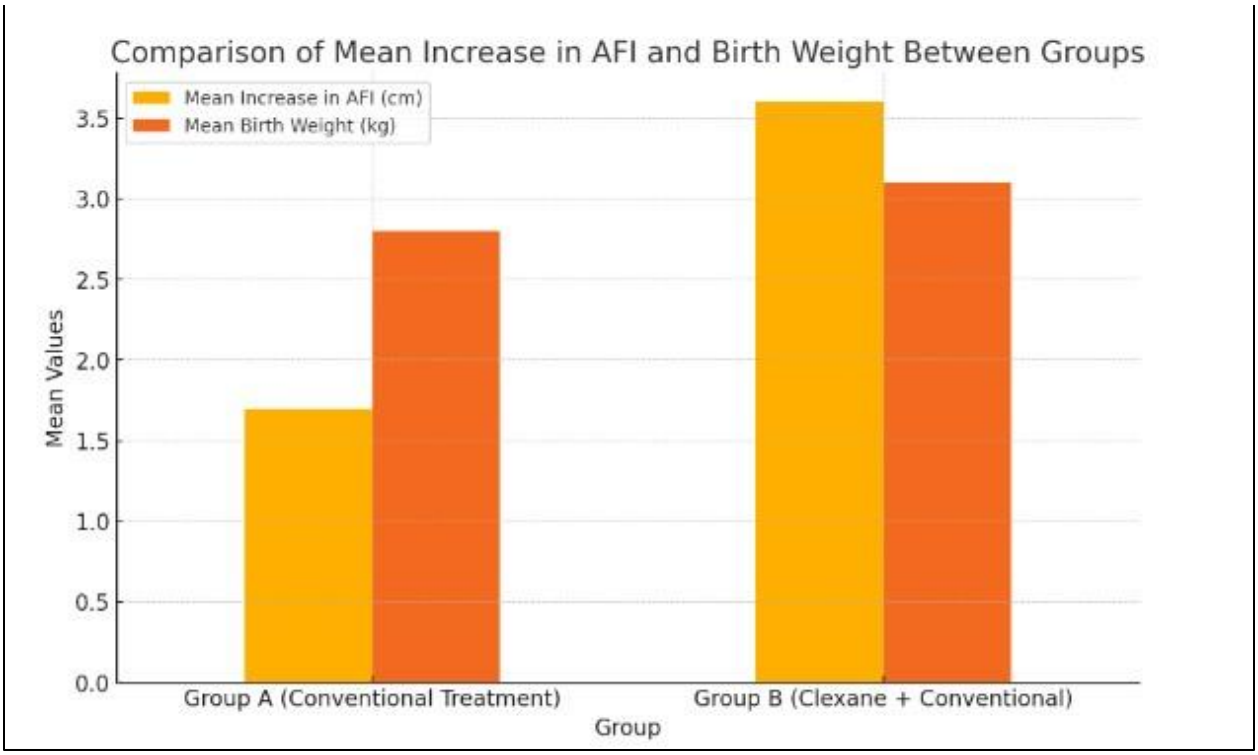
(Table- I) AFI Improvement and Neonatal Outcomes

Treatment Group	Mean AFI Increase (cm)	Mean Birth Weight (kg)	NICU Admissions (%)	Success in Lower BMI (<30)	Success in Higher BMI (>30)	Significance (p-value)
Group A (Conventional Treatment)	1.7	2.8	35%	Yes	No	0.006

Group B (Clexane + Conventional)	3.6	3.1	20%	Yes	Yes	<0.001

In the conventional treatment only of women in Group A, a mean AFI increase was noted during follow-up over the four weeks with 1.7 cm. The neonatal outcome of this group is moderately established since it indicated birth weight at a mean average of 2.8 kg with an average rate of NICU admissions set at 35%. However, the improvement of AFI was more evident in those women with low BMI (less than 30). Those with higher BMI, more than 30 improved less, perhaps because they have underlying metabolic factors, such as hypertension, which can influence blood flow at the placental bed as well as influence AFI response. It seems then that conventional treatment does enhance AFI; however its effectiveness is confined and that is especially noted in higher BMI and hypertension patients.

However, the added treatment of conventional care among Group B where Clexane was supplemented did provide statistical difference between the increments of AFI values in at p values <0.001. A more promising improvement in amniotic fluid levels beyond the group treated conventionally alone than Clexane supplementation presented in which it may potentially have a beneficial effect beyond people of lesser and BMI individuals as its benefit on larger-scale generalized usage potential will be higher. Neonates from Group B mothers were found to have an average birth weight that was threefold higher, averaging at 3.1 kg; at 20%, this admittance rate into the NICU was highly improved. The inclusion of Clexane will enhance AFI and would therefore positively contribute to neonatal outcome and very likely be so in that uteroplacental perfusion is enhanced, thereby enhancing fetal development and morbidity-related conditions that would require treatment in the NICU.



(Figure-I) Comparison of AFI Increase Across Treatment Groups

Below is the bar chart indicating a comparison of the two groups in terms of mean AFI increase. From the figure, it can be seen that Group B (Clexane + Conventional) had a higher mean AFI increase than Group A (Conventional Treatment). This shows that Clexane is an effective treatment for oligohydramnios.

In this study, maternal BMI and hypertension were shown to influence AFI improvement. Women with a BMI of more than 30 showed a significantly lower improvement in AFI compared to those with a lower BMI (<30). Similar findings were seen in women with hypertension whose AFI responses to conventional treatment seemed to be blunted, suggesting that these factors may be impairing placental function and limiting the effects of treatment. In Group B, Clexane appeared to counteract these adverse effects somewhat since the BMIs both improved the AFI in addition to the hypertension women, and it thus suggests that the use of Clexane would indeed have a positive effect even when complicating factors, such as obesity and hypertension, are observed.

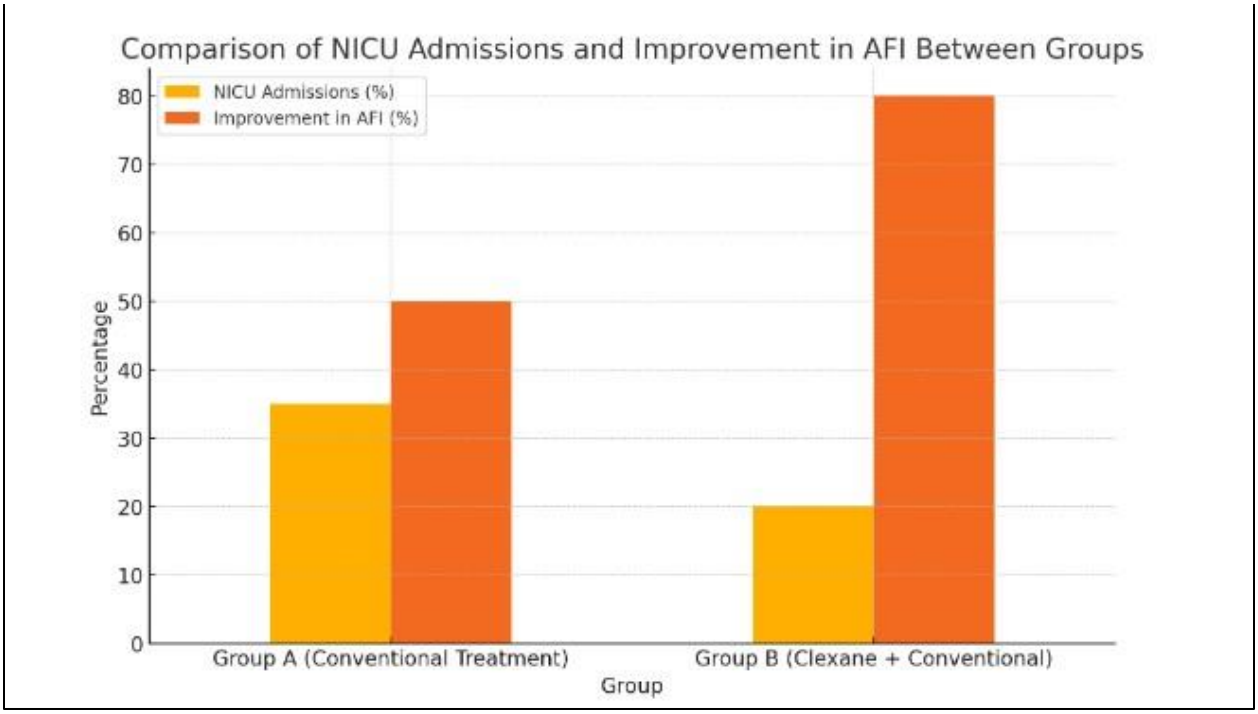
(Table-II) Maternal Factors and AFI Improvement

Maternal Factor	Group A AFI Improvement (%)	Group B AFI Improvement (%)	Significance (p-value)

Lower BMI (<30)	60%	80%	0.006
Higher BMI (>30)	40%	70%	0.02
Hypertension	30%	65%	0.01

The results showed that Group B had higher AFI improvement rates in both BMI categories, with 80% of women in the lower BMI group and 70% in the higher BMI group experiencing a significant increase in AFI. Women with hypertension in Group B also showed greater improvement compared to those in Group A, further supporting the hypothesis that Clexane's anticoagulant properties may help overcome some of the limitations posed by maternal health conditions.

The study also assessed neonatal outcomes, focusing on birth weight and the need for NICU admission. Neonates born to mothers in Group B had a significantly higher mean birth weight (3.1 kg) compared to those in Group A (2.8 kg), with a p-value of 0.01. Furthermore, the rate of NICU admissions was lower in Group B, with only 20% of neonates requiring intensive care compared to 35% in Group A (p=0.03). These findings suggest that Clexane not only improves AFI but also contributes to better overall fetal health, possibly due to enhanced placental perfusion leading to improved oxygen and nutrient delivery to the fetus.



(Figure-II) NICU Admission Rates by Treatment Group

The bar chart below illustrates the differences in NICU admission rates between the two groups, with Group B showing a significantly lower rate of NICU admissions compared to Group A.

Throughout the study, safety monitoring was conducted to assess any adverse effects related to the use of Clexane. No significant adverse effects, such as excessive bleeding or allergic reactions, were reported in either group. This finding supports the safety of Clexane when used in combination with conventional treatment for oligohydramnios. The absence of adverse effects further strengthens the case for incorporating Clexane into clinical practice for the management of this condition, particularly in high-risk pregnancies where AFI is critically low.

DISCUSSION

Findings of this study make Clexane a good adjunctive therapy for treatment of oligohydramnios after 28 weeks of gestation. Significant improvement in the AFI among Group B patients over Group A (3.6 cm vs. 1.7 cm) has been found in several previous studies that pointed toward LMWHs being the drugs with potential in use for obstetric care and beyond thromboprophylaxis. It seems that Clexane improves uteroplacental perfusion, which would contribute to a more important increase in AFI. This result may reduce the adverse perinatal risks of oligohydramnios, such as fetal growth restriction and preterm birth [19, 20].

The findings highlight the potential of Clexane to overcome limitations in conventional management of oligohydramnios, which includes hydration therapy, bed rest, and amnioinfusion. Although widely applied, these methods demonstrate inconsistent effectiveness, and are rarely effective for women with complicating high-risk pregnancies such as obese or hypertensive women [21,22,23]. This research contributes to the already developed findings by Jacobson et al. regarding the effectiveness of using enoxaparin that demonstrated an improvement in outcomes during high-risk pregnancies and explained that Clexane's action in anticoagulants and anti-inflammatory aspects can indirectly benefit the fetuses through the influence on AFI by improving uteroplacental blood flow.

Interestingly, in Group B, a good consistency was found throughout with the efficacy of increasing the value of AFI that could be due to treatment by Clexane when considering both BMI levels. This is important information because managing oligohydramnios when elevating BMI poses a threat that metabolic demands and potentially created hypertension compromise placental functions and AFI levels [24, 25]. While conventional treatments in and of themselves seem less than optimally effective alone for patients with high-BMI, the addition of Clexane seems to lessen these limitations, so such therapy might be a potential candidate as an alternative, potentially more appropriate in this type of patient.

Neonatal outcomes also presented an impressive effect where neonates in Group B had higher mean birth weights of 3.1 kg, whereas neonates admitted to NICU stood at a lower rate of 20% as compared to neonates in Group A. These neonatal outcomes further indicate that improved placental perfusion with Clexane can eventually lead to better fetal growth and a reduced risk of neonatal complications as compared to results from Sultana et al. showing that increased uteroplacental perfusion has been related to improved neonatal outcome in pregnancies considered at a high risk [7]. The lower admission rate in Group B may also be attributed to the increased supply of oxygen and nutrients to the fetus, which is essential for the maintenance of fetal growth in cases of oligohydramnios [26]. The present study validates the regional findings that adding Clexane to clinical practice for AFI may offer a useful solution especially in regions with limited availability of advanced prenatal interventions.

The absence of significant adverse effects in both treatment groups further strengthens the safety profile of Clexane in the treatment of oligohydramnios. No significant bleeding complication or allergic reaction was reported during monitoring, which indicates that Clexane does not carry a risk of adverse effects when used as an adjunct to standard management in late gestation. This is also in line with previous studies, which indicated that LMWHs such as enoxaparin have been proven to be safe and well-tolerated in pregnancy, particularly in high-risk patients.

Despite its promising results, this study has several limitations. The four-week follow-up period of this study may not account for the full effects that Clexane exerts on AFI and neonatal outcomes. Future studies may extend the follow-up period to determine whether such benefits persist and explore further long-term neonatal outcomes, in addition to analyzing parameters of dosage and duration that best apply to Clexane in maximizing efficacy within different patient populations. Furthermore, multicentric studies with an adequate sample size could evaluate the utility of Clexane in a variety of clinical and demographic settings.

CONCLUSION

This randomized controlled trial used the study methodology to establish rigorously the efficacy of Clexane in enhancing AFI in pregnant women suffering from oligohydramnios. Use of randomization, blinding, and multivariate analysis was made to conduct the study with high internal validity to reduce bias and confounding. The present study therefore aims to give robust evidence by comparing the outcomes between a control group that received conventional treatment and an intervention group receiving Clexane if this latter could be valuable in managing oligohydramnios and therefore in improving neonatal outcome.

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