Comparative Study Between Vaginal Progesterone Alone or Combined with Aspirin in Prevention of Recurrent Preterm Birth

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Abstract

Background: Preterm birth (PTB) carries the greatest risk of perinatal morbidity and mortality because of its neurological and developmental consequences later in life.

Objectives: To evaluate the efficacy and safety of vaginal progesterone alone or in combination with aspirin for the prevention of recurrent spontaneous PTB.

Methods: This was a randomized, double blind, placebo controlled trial conducted on 256 pregnant females with previous history of spontaneous PTB who randomly divided into 2 groups; **Group 1:** 128 females received combined vaginal progesterone plus aspirin, and **Group 2:** 128 females received vaginal progesterone plus placebo started at 16-20 weeks' gestation. The primary outcome was the occurrence of PTB prior to 34 weeks' gestation. Secondary outcomes were maternal: (1) harm to the mother from intervention, (2) maternal infection or inflammation, (3) prelabour rupture of membranes, (4) maternal mortality, and neonatal: (1) The gestational age at birth (2) respiratory morbidity, (3) birth weight, (4) infection (neonatal sepsis), (5) gastrointestinal morbidity, (6) early neurodevelopmental morbidity (within one month of delivery), (7) harm to the neonate from intervention, (8) perinatal mortality.

Results: Both groups showed non-significant difference regarding socio-demographic data. Rates of deliveries <34 weeks were 44% and 49% in group 1 and 2, respectively (p=0.072). Subgroup analysis according to the gestational age at delivery also done to detect if the drug combination (progesterone with aspirin) can have more effect at certain gestational age than others but the results were also non-significant. When considering other secondary outcomes, the rate of preterm rupture of membranes, neonatal birth weight, GIT morbidity, and perinatal deaths all showed significant difference between both groups (p<0.05) with cases received both progesterone and aspirin had improvement of theses parameters.

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Conclusion: Combination of vaginal progesterone and aspirin didn't significantly reduce the risk of recurrent spontaneous PTB than vaginal progesterone alone but had better neonatal outcomes by decreasing perinatal morbidity and mortality that might be secondary to reducing the rate of preterm rupture of membranes.

Keywords: PTB, Progesterone, Aspirin, Neonatal outcomes.

Introduction

The highest risk of perinatal and neonatal mortality and morbidity was associated with preterm birth (PTB) (defined as delivery at gestational age < 37 weeks) due to its developmental and neurological repercussions in later life [1].

The gestational age at delivery is directly proportional to the survival rate of preterm infants. Survival rates are less than 50% before 24 weeks and reach 95% by 33 weeks [2].

The identification of cases at risk for recurrent PTB can enable successful intervention, thereby reducing the burden on the family and community. Consequently, scientists are motivated to conduct trials in order to identify not only a single drug regimen, but also to potentially use a drug combination to achieve the most effective prevention [3].

Numerous interventions have been proposed to prevent PTB, such as home uterine monitoring, psychosocial interventions, risk scoring systems, aspirin, tocolysis, progestogens, optimal birth spacing, bed rest, activity restriction, health system interventions (packages of antenatal care, specialized antenatal clinics, midwifery-led care), nutritional interventions, cervical cerclage, and cervical pessary. Regrettably, numerous of these interventions have been shown to be ineffective in reducing the risk of PTB in both singleton and twin gestation [4,5].

Nine years ago, the United States Food and Drug Administration (FDA) authorized progesterone for the prevention of PTB. The majority of studies indicate that pregnant women who are treated with progesterone experience significant reductions in perinatal mortality and major morbidity, irrespective of the method of administration [5].

At present, the ACOG advises the vaginal progesterone administration to women who have a singleton gestation, a transvaginal cervical length of less than 25 mm, and no spontaneous PTB history at 18–22 weeks of gestation. This recommendation was recently revised in 2021 [6].

Aspirin was an additional medication that was evaluated for its potential to prevent PTB. It was recommended for use in at-risk pregnancies in numerous studies, with implementation commencing at 12 weeks gestation. It has been reported that aspirin resulted in improved placental implantation, while defective placentation may be one of the theories in this regard [7].

Our study conducted to detect the vaginal progesterone safety and efficacy either alone or in combination with aspirin in the prevention of recurrent spontaneous PTB.

Methods

This was a randomized, double blinded, placebo controlled trial held in the department of Obstetrics and Gynecology at Menoufia University Hospitals where the ethical committee of the University approved the protocol in January 2022 and after that registered at Clinical Trials.gov (https://clinicaltrials.gov/) as (NCT05319834).

Inclusion criteria: Women of any age, parity and gestational age between 16 to 20 weeks who were carrying a healthy singleton pregnancy in the current pregnancy and had a previous history of one or more spontaneous PTB in a singleton pregnancy at a gestational age between 24 and 36+6 weeks. Spontaneous PTB was defined as PTB that occurred following spontaneous contractions with intact membranes or spontaneously ruptured

membranes followed by PTB.

Exclusion criteria: A history of PTB due to cervical incompetence, medical disorder complicating a previous pregnancy, current cervical cerclage, known fetal anomaly, major chronic medical disorder (For example; chronic renal disease, chronic hypertension, and pregestational diabetes mellitus, as these conditions would increase the PTB risk and potentially confound the study outcome), known allergy to aspirin or progesterone, known liver disease, established preterm labor with advanced cervical dilatation (>4 cm), ruptured fetal membranes, and a short cervix <1cm. Women who presented at the outpatient clinic, emergency room, or were referred from other hospitals were eligible for the trial. One of the authors has conducted counseling on the benefits of the trial and its impact on the family and community. All participants have the right to withdraw from the trial at any point during the treatment process. The CONSORT guidelines were adhered to and implemented.

The medical research officer at the hospital prepared sealed, numbered opaque envelopes to conceal the trial sequence, which obtained by randomly assigning the included women to two trial groups in a 1:1 ratio utilizing a computerized random number table generator (MedCalc© version 13). An assignment for a single patient was inside each envelope.

Women were randomly assigned to either vaginal progesterone in combination with aspirin (Group 1) or vaginal progesterone in combination with a placebo (Group 2). Progesterone was administered to all women in the trial in the form of 200 mg vaginal suppositories every 12 hours (Prontogest® 200mg micronized vaginal suppositories, Marcyrl Pharmaceutical Industries/ Industrial zone – West Extension – Block 20016 El Obour City – Egypt). In group 1, aspirin administered once daily in a 100-mg dose in conjunction with progesterone (Aspirin® protect Memphis Co. for pharmaceuticals / Bayer Bitterfeld GmbH – Germany), while in group 2, an oral placebo (manufactured in a standard manner to resemble an aspirin tablet in size and shape) was administered. Administration initiated at 16 to 20 weeks' gestation and continued until 36 weeks or delivery, whichever occurred first. All cases advised to have additional bed rest periods and also instructed on the PTB symptoms. Antenatal care managed at 2-week intervals until delivery.

For all participants: A comprehensive history is obtained, with a particular emphasis on high-risk factors for PTB including past medical, surgical, and obstetric history, including full details of previous pregnancies (mode of conception, gestational age at delivery, cause and course of PTB, onset and mode of delivery, neonatal outcome, and any associated maternal or fetal complications). An account on the current pregnancy (mode of conception, estimated gestational age from the LMP, or an early pregnancy ultrasound) also obtained.

Physical examination: General examination, including maternal BMI, pulse, temperature, and blood pressure. For local examination, speculum was done to assess cervical dilation for cases presented with pelvic heaviness and ultrasound done for cervical measures and to exclude fetal anomalies.

Routine antenatal laboratory investigations, such as random blood sugar, urine analysis, full blood count, blood group and Rh typing.

Gestational age at delivery, mode of delivery, neonatal outcomes (Apgar score, birth weight, NICU admission, postpartum complications, and neonatal morbidity or mortality), drug side effects and maternal complications during delivery (if present) were all documented.

US Examination:

All patients underwent US using convex transducer with frequency of 2.5-10 MHz (Mindray 2200 digital Ultrasonic imaging system, China) with transabdominal probe

3.5 MHz and transvaginal probe 8 MHz before being enrolled in the trial to confirm their eligibility and cervical assessment also performed to exclude cervical insufficiency as being a cause of previous PTB. Further assessments were carried as per antenatal care.

Outcome:

The primary outcome was the occurrence of PTB prior to 34 weeks of gestation. As per ACOG practice bulletin no. 127 (2012), a 60-minute observation period was utilized to define preterm labor as the persistence of at least two symptomatic uterine contractions within a 10-minute period, as well as cervical changes (cervical dilation between 0 and 3 cm for nulliparous and from 1 to 3 cm for multiparous, with cervical effacement <50%) [8]. Secondary outcomes were either maternal that included: (1) harm to the mother from intervention, (2) maternal infection or inflammation, (3) prelabour rupture of membranes, and (4) maternal mortality, or neonatal that included: (1) The gestational age at birth which is classified according to standard subcategories, which include extremely preterm (gestation from <28+0 weeks), very preterm (gestation from 28+0 weeks to <32+0 weeks), and moderate to late preterm (gestation from 32+0 to <37+0 weeks), (2) respiratory morbidity, (3) birth weight, (4) infection (neonatal sepsis), (5) gastrointestinal morbidity, (6) early neurodevelopmental morbidity (within one month of delivery), (7) harm to the neonate from intervention, and (8) perinatal mortality. Other related outcomes were: admission to the NICU, and any adverse drug effects.

Statistical analysis:

We assumed an anticipated increase of 15% in the rate of reduction of PTB with the addition of both drugs, increasing the rate of prevention of PTB to 30-35%; accordingly, at a study power of 95% and two-tailed alpha of 0.05, a minimum total sample size of 256 women is required, considering a possible dropout rate of 10% of cases. The Statistical Package for the Social Sciences (SPSS) version 26 (SPSS Inc. Released 2018) was employed to collect, tabulate, and conduct statistical analyses of the data.

In order to determine whether the quantitative data were normally distributed, the Kolmogorov-Smirnov test was implemented. The Student's t-test was employed to compare the data if they were normally distributed, and the results were expressed as the mean SD. The Mann-Whitney U-test was employed to compare the data if they were not normally distributed, and they were expressed as the median (range). In order to assess qualitative data discrepancies, Fisher's exact test or chi-square test was implemented. Significant differences were defined as P-values <0.05, while highly significant differences were defined as P <0.001.

Results

Two hundred and fifty-six women were randomized: 128 received progesterone with aspirin, and 128 received progesterone with placebo. There were 11 (8.6%) cases in group 1 and 16 (12.5%) cases in group 2 excluded from final analysis due to discontinuation of treatment. The treatment, randomization, and follow-up of the cases are illustrated in **Figure 1.**

Table 1 Illustrates the baseline characteristics of the study participants. The parameters assessed did not exhibit any significant differences among both groups.

As regard the gestational age at delivery, rate of deliveries <34 weeks were 44% and 49% in group 1 and 2, respectively with insignificant difference (p=0.072). Also the difference among both groups regarding deliveries ≥ 34 weeks was insignificant (56% in group 1 versus 51% in group 2, p=0.0.87). Furthermore, no significant difference among both groups regarding deliveries more than 37 weeks as illustrated in **Table 2**.

Maternal outcomes were shown in **Table 3**;

there were non significant differences in maternal need for admission, tocolytic therapy or complications among both groups.

The neonatal outcomes demonstrated in **Table 4**. Progesterone with aspirin group had significantly better neonatal outcomes regarding the neonatal birth weight with lower gastrointestinal morbidity and perinatal death, but with no significant differences between both groups regarding other parameters including NICU admission.

Discussion

The large contributor to the perinatal morbidity and mortality worldwide was recurrent spontaneous PTB, which always motivated the need for additional preventive methods **[1]**.

Survival in preterm is directly related to gestational age at delivery; with less than 50% survival before 24 weeks and increased up to 95% by 33 weeks' gestation **[9]**.

Progesterone for prevention of PTB was approved by the United States Food and Drug Administration (FDA) nine years ago. Most studies suggest a significant risk reduction of perinatal mortality, and major morbidity among pregnant women treated with progesterone regardless of its route of administration **[10]**.

In the past, it was suggested that the action of progesterone was through nuclear receptors; however, it is now clear that some of the actions of progesterone are mediated through membrane receptors as well. Several studies have demonstrated a number of actions that could contribute to prevention of PTB. These actions may be seen at the following four different levels: (i) reducing cervical stromal degradation, altering the barrier to ascending infection, inhibiting cervical ripening and improving cervical length in patients with a short cervix; (ii) decreasing the concentration of myometrial oxytocin receptors, reducing contraction frequency and possibly acting as a tocolytic agent; (iii) attenuating the response to hemorrhage and inflammation in the decidua; and (iv) suppressing prostaglandin synthesis in fetal membranes and in the placenta, reducing apoptosis and altering estrogen synthesis. Additionally, progesterone alters endocrine-mediated effects in the fetus **[11]**.

Given that prophylactic intervention to prevent PTB entails a long duration of progesterone administration, less invasive forms of administration are preferred. Vaginal administration is characterized by very high endometrial concentrations because it avoids the first-pass metabolism prior to reaching the genital tract; so we prefer its use for our patients **[11]**. Data regarding the optimal route, dose or duration of progesterone are still lacking, and it remains unknown whether there is a dose–response relation between progesterone and its action to reduce PTB.

Despite the use of progestagens, at least one third of the women will have a recurrent spontaneous PTB, suggesting that multiple underlying mechanisms contribute to its pathogenesis **[12]**.

It was suggested that utero-placental ischemia plays a major role in the pathogenesis of spontaneous PTB. Placental vascular pathology and placental bed pathology are common findings in women with a spontaneous PTB **[13]**. Also, abnormal angiogenic/anti-angiogenic profile in maternal plasma is seen in a subset of patients with spontaneous PTB, and increased resistance at mid-trimester Doppler measurement of uterine artery flow provides an increased risk of spontaneous PTB **[14]**. These findings suggest an overlap of PTB with other ischemic placental diseases as pre-eclampsia.

Placental ischemia, as being one of the causes of spontaneous PTB, makes suggestions that any intervention to improve the placental blood flow might be effective in reducing the number of cases of recurrent PTB **[7]**.

One of these drugs is aspirin which considered safe in pregnancy and was already widely tested in pregnant women in other indica-

tions. Therefore, if the current study could prove aspirin to be effective in reducing recurrent spontaneous PTB, then it would be possible to implement in women with positive history of one or more spontaneous PTB.

Our study conducted to assess the difference in efficacy between vaginal progesterone when combined with aspirin vs vaginal progesterone when used alone in reducing the rate of recurrent spontaneous PTB. As the primary outcome was the occurrence of PTB prior to 34 weeks of gestation, we failed to find any favor for adding aspirin to progesterone when compared with using progesterone alone with percentage of deliveries 44 and 49% in group 1 and 2, respectively, (p=0.072; the primary outcome). Also, the difference among both groups regarding overall rates of delivery ≥ 34 weeks wasn't statistically significant (56% in group 1 versus 51% in group 2, p=0.087). We also did subgroup analysis according to the gestational age at delivery with the aim to find if the drug combination (progesterone with aspirin) can have more effect at certain gestational age than others but unfortunately, we couldn't prove any significant differences among both groups regarding deliveries at <28 weeks , 28-32 weeks, 32-34 weeks, 34-37 weeks and >37 weeks gestation (p>0.05; secondary outcome). These findings were in agreement with **Jessel et al., [15]** who found no reduction in the rate of PTB in any subgroup treated with aspirin as stratified by gestational age at delivery, type of PTB, or risk-group, with the exception of PPROM <35 weeks, a finding of doubtful significance given multiple comparisons. As attributable risk of PTB was high and aspirin started relatively late, possibly limiting the generalizability of their findings.

In agreement with **Jessel et al., [15]** our study showed significant difference in preterm rupture of membranes among both groups with 6 cases (4.7%) in (progesterone and aspirin) group vs 15 cases (11.7%) in (progesterone and placebo) group (p=0.044). These findings also reported by **Allshouse et al., [16]** who observed an effect size for aspirin for both low- and high-risk women as a PTB prevention strategy, although not reaching significance. Another study also reported that preterm rupture of membranes is linked to an increased risk of PTB **[17]**.

These findings were inconsistent with **Andrikopoulou and his colleagues [18]** who included 2543 women, 1262 (49.6%) received low-dose aspirin and 1281 (50.4%) received placebo. Baseline characteristics were similar between groups, except for marital status. The rate of spontaneous BTB <34 weeks was 1.03% (n = 13) and 2.34% (n = 30) in the low-dose aspirin and placebo group, respectively (odds ratio, 0.43, 95% confidence interval, 0.26-0.84). Additionally, the rate of spontaneous preterm birth <37 weeks was 6.58% (n=83) in the low-dose aspirin group and 7.03% (n = 90) in the placebo group (odds ratio, 0.97, 95% confidence interval, 0.71-1.33), and the rate of overall preterm birth <37 weeks was 7.84% (n = 99) in the low-dose aspirin group and 8.2% (n = 105) in the placebo group (odds ratio, 0.97, 95% confidence interval, 0.72-1.31). After adjustment for variables that were clinically relevant or statistically significant, including body mass index, race, tobacco use, marital status, and education level, there was a significant reduction in spontaneous preterm birth <34 weeks in the low-dose aspirin group (adjusted odds ratio, 0.46, 95% confidence interval, 0.23-0.89). The rates of overall preterm birth <34 and <37 weeks and spontaneous preterm birth <37 weeks were similar in women who received low-dose aspirin compared with placebo. So they concluded that aspirin was associated with a substantial decrease in spontaneous PTB <34 weeks in healthy nulliparous women without co-morbidities.

The study of **Hoffman et al., [19]** also found rate of PTB occurred in 5787 women who received aspirin and 5771 women who received placebo to be 11.6% in women randomized

to aspirin and 13.1% for those randomized to placebo (Relative Risk [RR], 0.89; 95% CI, 0.81 to 0.98; Risk Difference, −0.02; 95% CI, −0.03, −0.01) which is not statistically significant.

Our study also found significant difference between both groups regarding fetal weight at delivery with mean fetal weight of 2772.66 and 2379.3 gm in (progesterone and aspirin) and (progesterone and placebo), respectively ($p < 0.001$). These results were different from that reported by **Silver et al., [20]** who did not find significant impact of using aspirin on birth weight with mean values at delivery of 2437 ± 808 vs 2570 ± 554 gm in the aspirin and placebo groups, respectively.

Regarding NICU admission, 17 neonates (14.5%) vs 19 neonates (16.9%) were in need for admission in (progesterone and aspirin) and (progesterone and placebo), respectively ($p=0.095$). Similar non significant NICU admission were reported in 2015 by Martinez de **Tejada et al. [21]** with 29.8% and 25.4% of the neonates in the progesterone and placebo groups needed NICU admission.

Our study showed also significant difference between both groups regarding gastrointestinal morbidity, 6 (5.1%) cases vs 9 (8%) cases in (progesterone and aspirin) and (progesterone and placebo), respectively ($p=0.046$). Low-dose aspirin (started at < 16 weeks gestation) was linked to a higher reduction in perinatal death and other adverse perinatal outcomes, according to the meta-analysis by **Roberge et al. [22]**.

Perinatal deaths reported in 3 (2.5%) cases in (progesterone and aspirin) and 8 (7.1%) cases in (progesterone and placebo) groups ($p=0.045$). This significant difference in both groups can be attributed to less neonatal morbidity (GIT) shown in (progesterone and aspirin) group.

Taking the medical disorders that could arise during pregnancy into consideration, our study detected non significant difference between both groups regarding pre-eclampsia. Similar results were also detected by **Hoffman et al., [19]** with hypertensive pregnancy disorders noted in 6.1% and 5.6% of patients in the aspirin and placebo groups, respectively.

One of the exclusion criteria considered among our patients was history of PTB due to cervical incompetence. Accordingly, non of our patients having cervical length <2.5 cm. **O'Hara et al., [23]** reported that one of the most potent markers of PTB in women carrying singletons and twins is a shorter cervix. The probability of spontaneous PTB increases with decreased cervical length. Moreover, **Romero et al., [11]** came to the conclusion that the probability of spontaneous PTB increased with decreased cervical length.

In the present study, patients with cervical cerclage were excluded in order to measure the solely effect of progesterone either alone or with aspirin. Controversy about the interaction between cerclage and progesterone remains. **Rebarber et al., [24]** reported a benefit from 17α-hydroxyprogesterone in women with cerclage. On the contrary, **Berghella et al., [25]** showed no additional benefit of 17α-hydroxyprogesterone caproate for the prevention of PTB in women who had ultrasound-indicated cerclage if their cervical length was <25 mm, but if these women did not have cerclage the drug reduced previable and perinatal mortality. The additive effect of progesterone and cerclage for the prevention of PTB depends on different factors, including prior obstetric history, risk factors for PTB and the degree of cervical shortening; therefore, while a cerclage suture may be better for women with a shorter cervix, progesterone may be more beneficial for women with lesser degrees of cervical shortening [11]. More research regarding the mechanisms of progesterone and cerclage in PTB may help clinicians to understand how these two interventions can be used together.

The strengths of our study were: (1) : it is a randomized trial with well-designed method of randomization (computer based) and ad-

equate power calculations; (2) both patients and physician were blind regarding group assignment; (3) aspirin was tested at the usual doses used in previous studies to clinically confirm the hypothesis; (4) participants' outcomes were tracked until delivery to ensure the effect of implementation; (5) cervical status was taken at baseline; and (6) the outcomes were subdivided into primary and secondary for comparison and combination in any meta-analysis.

On the other hand, negative aspects could still be detected as: (1) the aetiology of premature uterine contractions (infection/inflammation?) was not considered before randomization; (2) aspirin was only used in combination with progesterone, so testing the effect of aspirin alone on spontaneous PTB was not done; (3) only one dose regimen of aspirin was used, although comparing the effect of different regimens may give different results; (4) one-center study (Menoufia University), future studies on multi-center bases may confirm and strengthen our results; (5) lack of funding with no cost-effectiveness analysis; (6) we were unable to determine the efficacy of this new combination for twins or preterm premature rupture of membranes due to their exclusion.

In conclusion, our data showed that although the combination of vaginal progesterone with aspirin failed to reduce the rate of recurrent spontaneous PTB, it was associated with significant reduction in the rate of preterm rupture of membranes as well as improvement of some neonatal outcomes (neonatal birth weight, GIT morbidity, and perinatal deaths). More data from different populations are needed to support our results.

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Figure legend

Figure (1): Flow chart of the study group.

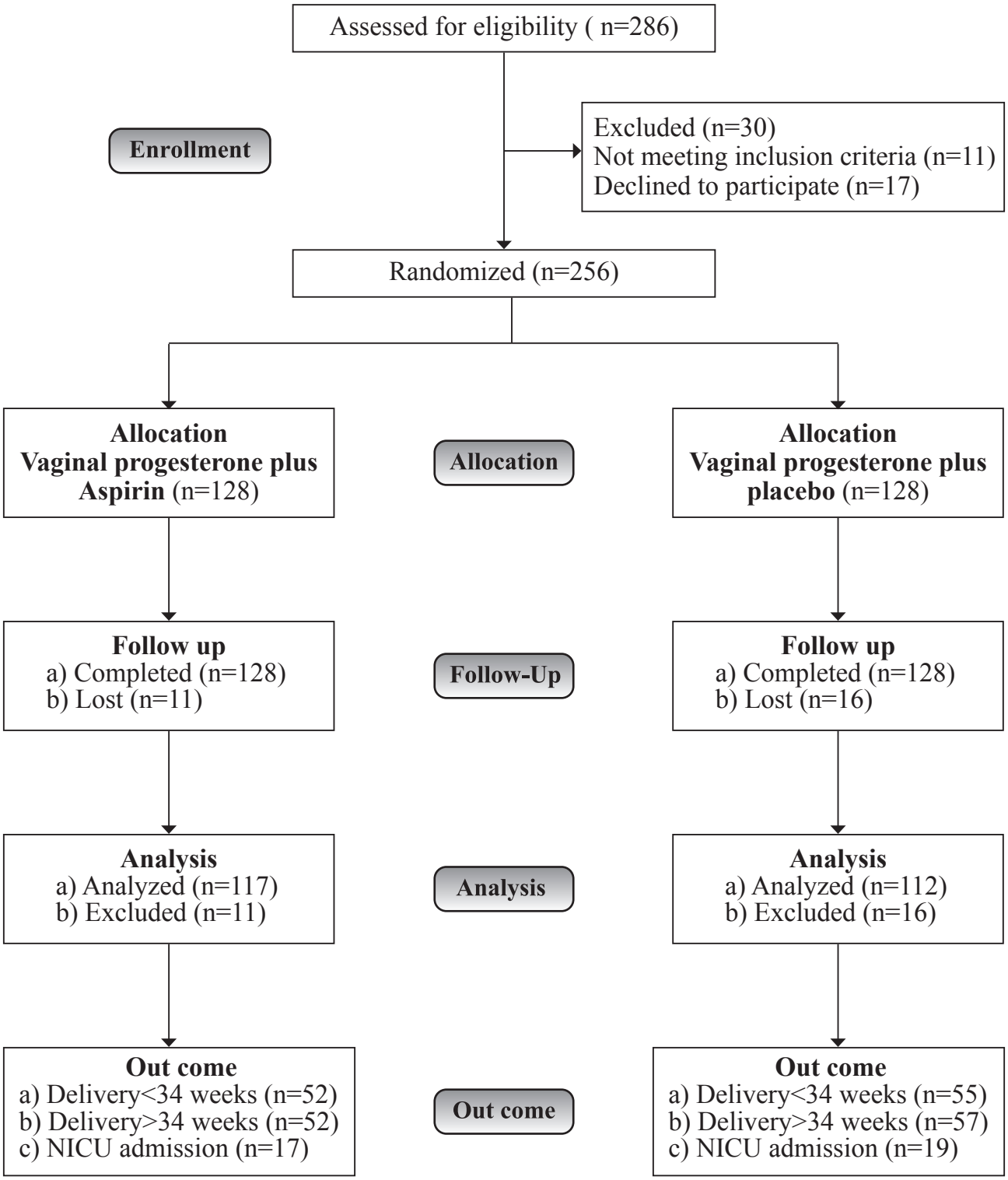

Table (1): Socio-demographic and clinical data of studied groups:

Variables	Progesterone with aspirin group (n =128)	Progesterone with placebo group (n =128)	P-value
Maternal age, years (Mean ±SD) Range	29.9±3.88 22-41	28.91±4.11 22-41	0.05
Parity (No., %) a) 2 times b) 3 times c) 4 times	62 (48.4) 57 (44.5) 9 (7.0)	68 (53.1) 48 (37.5) 12 (9.4)	0.478
BMI, kg/m^2 (Mean± SD) Range	28.05±1.981 24-38	28.07±2.392 25-35	0.955
History of PTB (No., %) a) Once b) Twice c) 3 or more	5 (3.9) 118 (92.2) 5 (3.9)	7 (5.5) 117 (91.4) 4 (3.1)	0.449
Mode of conception (No., %) a) Spontaneous b) Induction ovulation c) IVF	56 (43.8) 36 (28.1) 36 (28.1)	60 (46.9) 36 (28.1) 32 (25.0)	0.830
GA at randomization, days (Mean ±SD) Range	126.1±7 112-140	124.5±11 112-140	0.168
Cervical length in cm (No., %) a) 2.5-4b) b) >4	86 (67.2) 42 (32.8)	91 (71.1) 37 (28.9)	0.499
Medical disorders complicating pregnancy a) None b) Mild preeclampsia c) Sever preeclampsia d) Gestational DM	89 (69.5) 12 (9.4) 7 (5.5) 20 (15.6)	90 (70.3) 17 (13.3) 5 (3.9) 16 (12.5)	0.649

Table (2): Comparison between studied groups according to gestational age at delivery

GA at delivery (wks)	Progesterone with aspirin group (n =117)	Progesterone with placebo group (n =112)	P-value
All Deliveries < 34 w (No., %)	**52 (44)**	**55 (49)**	**0.072**
All Deliveries ≥ 34 w (No., %)	**65 (56)**	**57 (51)**	**0.087**
Delivery < 28 w	1 (0.8)	2 (1.7)	0.561
Delivery from 28 to <32 w	12 (10.24)	13 (11.6)	0.833
Delivery from 32 to <34 w	39 (33.3)	40 (35.7)	0.62
Delivery from 34 to <37w	39 (33.3)	34 (30.3)	0.065
Delivery ≥ 37 w	26 (20.3)	23 (20.5)	0.074

Table (3): Secondary Maternal outcomes according to treatment

Variables	Progesterone with aspirin group (n =128)	Progesterone with placebo group (n = 128)	P-value	Odds ratio (95% CI)
Admission for threatened PTB	47 (35.2%)	60 (46.9%)	0.057	0.614 (0.372-1.015)
Tocolytic therapy	47 (36.7%)	60 (46.9%)	0.099	0.658 (0.399 – 1.084)
Preterm rupture of membranes	6 (4.7%)	15 (11.7%)	0.044*	0.670 (0.139– 0.988)
Mode of delivery SVD CS	 71 (55.5%) 57 (44.5%)	 68 (53.1%) 60 (46.9%)	0.707	1.099 (0.672 -1.798)
Patients compliant to treatment	117 (91.4%)	112 (87.5%)	0.309	1.519 (0.676 – 3.416)
Patients discontinue treatment	11 (8.6%)	16 (12.5%)	0.309	0.658 (0.293 – 1.480)
Patients develop drug side effects	34 (26.6%)	36 (28.1)	0.779	0.924 (0.533 – 1.602)
Harm to mothers from intervention	0 (0)	0 (0)	---	---
Maternal infection	0 (0)	0 (0)	---	---
Maternal mortality	0 (0)	0 (0)	---	---

*Significant statistically

Table (4):Secondary fetal outcomes according to treatment

Variables	Progesterone with aspirin group (n =128)	Progesterone with placebo group (n = 128)	P-value	Odds ratio (95% CI)
Neonatal weight (gm) Mean ±SD Range	 2772.66±519 1100-3500	 2379.3±512.7 800-3500	<0.001*	0.988 (0.988 – 0.999)
Admission to NICU	17 (14.5%)	19 (16.9%)	0.095	0.435 (0.160-1.183)
Respiratory morbidity	5 (4.2%)	9 (7%)	0.05	0.255 (0.069 -0.938)
Gastrointestinal morbidity	6 (5.1%)	9 (8%)	0.046*	0.255 (0.069 -0.938)
Neonatal sepsis	7 (5.9%)	8 (7.1%)	0.08	0.283 (0.076 – 1.054)
Perinatal death	3 (2.5%)	8 (7.1%)	0.045*	0.255 (0.069-0.038
Harm to offspring from intervention	0 (0)	0 (0)	---	---

*statistically significant