Progesterone Gel and Placebo were Equally Effective in Preventing Preterm Birth Among Women with Preterm Labor

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Research

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Abstract

Introduction The aim of this trial was to evaluate the effect of maintenance treatment with vaginal progesterone gel compared to placebo in preventing preterm birth after the onset of preterm labor.

Methods A randomised controlled trial in Sweden in 2009 – 18. Women with preterm labor were randomized to daily doses of progesterone gel 90 mg (n = 29) or placebo (n = 29) after standard treatment with intravenous tocolytics. Women with intravenous tocolytics alone served as controls.

Results The latency to delivery was 58 ± 34 days with progesterone and 64 ± 51 days with placebo (p = 0.83), compared to 2 ± 2 days in the control group (progesterone and placebo *vs* control p < 0.001). The rate of preterm birth before 34 weeks was 34 % after progesterone and 38 % after placebo (p = 0.34) compared to 100 % in the control group (p < 0.001 respectively). The composite neonatal morbidity (p = 0.65) and neonatal intensive care unit admission (p = 0.12) were comparable between the progesterone and placebo groups, but lower in these groups compared neonates of women in the control group (p < 0.001 respectively).

Conclusion Maintenance treatment with progesterone gel and placebo were equally effective in preventing preterm birth among women with preterm labor. Both progesterone and placebo prolonged pregnancy more effectively than intravenous tocolysis alone. We hypothesize, that the acidic gel base reinforced the biochemical barrier at the uterine cervix, which counteracted ascending pathogen invasion and subsequent inflammation and thereby delayed preterm birth. The present results suggest, that non-hormonal agents that reinforce the biochemical cervical barrier can be useful for the prevention of preterm birth in clinical practice.

Introduction

The global rate of preterm birth (PTB) – the main cause of neonatal, infant and child mortality up to 5 years age – is still 10 % [1]. Risk factors include psychosocial stress, malnutrition, low and high maternal age, multiple pregnancy, decidual bleeding, uterine infection due to ascending pathogen invasion, and alterations in the vaginal microbiome [2 – 7]. Current intravenous and oral tocolytic treatments do not prevent PTB, but are given with an aim to delay delivery for at least 48 hours to optimise the effect of antenatal corticosteroids for fetal lung maturation and allow for transport to a tertiary hospital with Neonatal Intensive Care Unit (NICU) expertise [8]. A cervical length (CL) ≤ 25 mm in early pregnancy is regarded as a primary predictor for PTB [9].

The connective tissue remodeling of the uterine cervix which precedes term and preterm labor is characterized by an increased density of macrophages in the cervical tissue, release of proinflammatory cytokines and prostaglandin E, a functional progesterone withdrawal, activation of metalloproteinase (MMP) enzymes, a changed proteoglycan composition with dispersion of collagen fibrils, and collagen degradation. These biochemical events lead to cervical effacement and dilatation that allow for childbirth [4 – 7, 10].

Progesterone is regarded as the primary hormone for pregnancy maintenance, but reports on prophylactic treatment with bioidentical progesterone or synthetic progestins such as 17α-hydroxyprogesterone caproate (17OH – PC) for the prevention of PTB are inconclusive [2]. Bioidentical progesterone has no androgenic effects that might affect the lipid metabolism or harm the fetus. Since oral progesterone is poorly absorbed because of the liver metabolism, daily progesterone injections would be painful, a transdermal progesterone preparation has not been available in obstetrics, vaginal treatment is used in clinical practice [2, 11]. Prophylactic treatment, which is recommended by the International Federation of Gynecology and Obstetrics (FIGO) for asymptomatic women with a previous PTB or a short CL, is effective according to some studies except from those with the largest sample size [2, 12, 13]. Extensive screening programmes are needed to evaluate prophylactic strategies since only 10–20 % of women with spontaneous PTB have a previous PTB [2, 9] and only 1 % of asymptomatic women have a CL ≤ 25 mm in early pregnancy [14].

Aim. The aim was to compare the effect of maintenance treatment with progesterone gel to placebo gel for the prevention of PTB after the onset of preterm labor (PTL). The participating women were randomized to the maintenance treatments after intravenous tocolytics according to standard clinical routines. We hypothesized, that progesterone would be more effective than the placebo [15]. Women who received intravenous tocolytics alone were identified in retrospect and served as a control group.

Materials And Methods

Trial design. This randomized controlled trial was conducted at the Obstetric Unit, Department of Women ´s and Children´s Health, Karolinska University Hospital and Karolinska Institutet, Stockholm, Sweden between December 2009 and January 2018.

Ethics approval

and registration. Ethics approval was obtained from the Regional Ethics Board for Medical Sciences in Stockholm in September 2007, No 2007-311-31. The trial was registered at the European Union Drug Regulating Authorities Clinical Trials (EudraCT), that participates in the World Health Organization (WHO) International Clinical Trial Registry Platform in September 2007, No 2007-003348-31, and was approved by the Swedish Medical Products Agency in May 2008, No 151:2008/30388. All treatments were performed according to the relevant clinical guidelines and regulations, and all participants were included after informed oral and written consent. Ethics approval for the control group of women, who received standard intravenous tocolytics alone in the same years 2009–18 was obtained from the Regional Ethics Board for Medical Sciences in Stockholm in April 2015, No 2014/255 – 31. Since data from the control group were collected in retrospect and presented on a group basis only, individual consent was not required.

Participant recruitment. Inclusion criteria were singleton pregnancy, intact fetal membranes, and spontaneous PTL between 24 and 28 gestational weeks resulting in a CL < 25 mm determined by transvaginal ultrasound. Exclusion critera were multiple pregnancy, ruptured fetal membranes, cervical

dilatation, cervical cerclage, signs or symptoms of chorioamnionitis, previous uterine surgery, prophylactic progesterone treatment, intercurrent maternal diseases, pregnancy complications such as preeclampsia or gestational diabetes, intrauterine fetal growth restriction or fetal malformations (Fig. 1). The participants were informed about the randomized trial by an obstetrician at the hospital, and they received standard intravenous tocolysis before start of the treatments. Randomization was carried out after oral and written consent, using a computerised blocked system and with closed envelopes. Data were collected in retsrospect from the control group of women with identical inclusion and exclusion criteria who received standard intravenous tocolytics alone in the same years 2009–18. Preterm labor was uterine contractions ≥ 2/10 min for > 30 min according to cardiotocography (CTG) recorded in electronic obstetric records (Obstetrix, Cerner AB, Stockholm, Sweden), which resulted in a CL < 25 mm determined by transvaginal ultrasound carried out by a specialist in obstetrics and gynecology due to standardized criteria.

Interventions. The maintenance treatments were daily doses of vaginal progesterone gel (Crinone, 90 mg/dose, Merck KGaA, Germany) or daily doses of the placebo gel, which is an emulsion of oil and water with an acidic pH 3.0 (Replens, CampusPharma AB, Sweden). It was not possible to blind the gel packages due to practical reasons. The treatments started after standard intravenous tocolytics and continued until 34 + 0 weeks, rupture of the fetal membranes or childbirth whatever occurred first. In all years studied, standard intravenous tocolytics consisted of a bolus dose of the oxytocin receptor antagonist atosiban (Tractocile, Ferring Pharmaceuticals, Sweden) 6.75 mg followed by infusion of 300 µg/min during 3 hours and thereafter 100 µg/min until 48 hours. Alternatively, a β2-adrenergic receptor agonist terbutaline (Bricanyl, AstraZeneca PLC, Great Britain) 5 µg/mL was given for 48 hours according to the individual obstetrician´s choice. All women received two doses of betamethasone (Betapred, Swedish Orphan Biovitrum AB) 12 mg intramuscularly 12 — 24 hours apart for fetal lung maturation. In line with standard clinical routines, the participants with PTL and intact fetal membranes did not receive prophylactic antibiotics. All women in active labor at a gestational age < 37 + 0 weeks received intrapartum prophylaxis with bensylpenicillin 3 g every 6 hours. All women in all groups were seen at least weekly by an obstetrician after discharge from the antenatal unit in case of regression of PTL.

Outcomes. The analyses included all randomized participants according to the intention to treat concept. We did not epect drop outs, since the participants were randomized after thorough informed consent and were seen frequently by an obstetrician. The primary outcome latency to delivery was calculated from the first gel dose to childbirth in the treatment groups, and from the start of intravenous tocolysis to childbirth in the control group. The secondary outcomes were delivery ≤ 7 days, rates of PTB < 34 weeks and < 37 weeks, neonatal birth weight (BW), composite neonatal morbidity, NICU admission and length of NICU stay. Composite neonatal morbidity was Apgar score < 7 at 5 min, the incidence of neonatal respiratory distress syndrome (RDS), intraventricular hemorrage (IVH), necrotizing enterocolitis (NEC) and sepsis ≤ 7 days, taken together with retinopathy of prematurity (ROP) and neonatal death during NICU stay. Neonatal RDS was defined by clinical diagnosis of type I RDS and a requirement of oxygen therapy for at least 24 hours. Maternal adverse effects such as fatigue, headache, or intrahepatic cholestasis were monitored.

Sample size. We expected, that the latency to delivery would be 30 % longer after progesterone compared to placebo. According to a power analysis, a sample size of n = 29 in each group would be required to reach a significance of 5 % and power of 80 % [16].

Statistical analysis. Continuous data were analyzed using Mann Whitney U-test, and were presented as mean ± standard deviation (SD). Categorical data were analyzed with Chi^2-test and Fisher´s exact test when appropriate, and were presented as numbers and percentages. Confidence intervals and composite neonatal morbidity were analyzed with One way ANOVA. A two-tailed p value < 0.05 was considered significant.

Results

We evaluated the effect of maintenance treatment with vaginal progesterone gel (n = 29) compared to placebo (n = 29) in preventing PTB after the onset of PTL at an early gestational age. The maintenance treatments were given after standard intravenous tocolytics. Women with identical inclusion and exclusion criteria who received intravenous tocolytics alone (n = 29) were identified in retrospect and served as a control group. The rate of early PTB before 28 + 0 weeks was < 1 % of the n = 33 697 births at our hospital in 2009–18.

Maternal characteristics. Maternal characteristics are shown in Table 1. The demographic data were comparable between the groups. The participants in all groups had a medical history of a previous PTB in 25 % and first or second trimester spontaneous abortion in 25 % (data not shown). The mean gestational age at the beginning of the treatments, and at the start of tocolytics in the control group, was 26–27 weeks, where 82 % of the participants were included between 24–27 weeks and 8 % between 28–31 weeks. The CL (mean ± SD) at the beginning of treatment was 11 ± 5 mm in the progesterone group, 12 ± 5 mm in the placebo group, and 14 ± 7 mm at the start of tocolytics in the control group. The mean circulating level of the inflammatory marker C-reactive protein (CRP) was low ≤ 10 mg/L in all groups (data not shown).

Maternal outcome. Maternal outcome is shown in Table 2. The latency to delivery (mean ± SD) was 58 ± 34 days in the progesterone group and 64 ± 51 days in the placebo group (p = 0.83). The rate of PTB < 34 weeks was 34 % with progesterone and 38 % with placebo (p = 0.32), and the rate of PTB < 37 weeks was 52 % with progesterone and 45 % with placebo (p = 0.65). The compliance rates were high. One participant in each group had her treatment interrupted before 34 weeks after referral to another hospital, and both gave birth after 37 weeks. One woman in the progesterone group, who had an emergency cervical cerclage on maternal request after inclusion continued her progesterone treatment and gave birth at 34 weeks. No severe maternal side effects such as headache or intrahepatic cholestasis were reported. One woman in the progesterone group reported fatigue. In the control group, the latency to delivery was 2 ± 2 days (progesterone and placebo *vs* control p < 0.001), and the rate of PTB < 34 weeks was 100 % (progesterone *vs* control p = 0.01; placebo *vs* control p = 0.02).

Neonatal outcome. Neonatal outcome is shown in Table 3. The BW (mean ± SD) was 2471 ± 1078 g in the progesterone group and 2452 ± 1054 in the placebo group (p = 0.84). The composite neonatal morbidity was 72 % (21/29) after progesterone and 65 % (19/29) after placebo (p = 0.65). The rate of NICU admission was 31 % (9/29) after progesterone and 24 % (7/29) after placebo, and the mean length of NICU stay was 10 days in both groups (p = 0.59). Two neonatal deaths occurred during the NICU stay in the progesterone group and one in the placebo group. These neonatal deaths were caused by postnatally diagnosed severe malformations and chromosomal aberrations and were not associated with the different treatments. In the control group, the BW (mean ± SD) was 1023 ± 409 g (progesterone and placebo *vs* control p < 0.001), the composite morbidity was120 % (57/29) (progesterone and placebo *vs* control p < 0.001), the rate of NICU admission was 100 % (29/29) and the mean NICU stay 70 days (progesterone and placebo *vs* control p < 0.001). Two neonatal deaths occurred during the NICU stay.

Discussion

We have compared the effect of maintenance treatment with vaginal progesterone gel to placebo for the prevention of PTB among women with PTL at an early gestational age. The treatments started after standard intravenous tocolytics, and women with identical inclusion and exclusion criteria who received intravenous tocolytics alone served as a control group.

We found, that the effect of maintenance treatment with progesterone gel was comparable to the effect of the placebo, and the hypothesis was therefore rejected. The primary outcome latency to delivery and the secondary outcomes rate of delivery within 7 days, and rates of PTB before 34 and 37 weeks were comparable between the progesterone and placebo groups. As a consequence, neonates of mothers in the progesterone and placebo groups had comparable mean BW, composite neonatal morbidities, rates of NICU admission, and lengths of NICU stay. However, the maternal and neonatal outcomes in the progesterone and placebo groups differed markedly compared to the control group of women who received standard intravenous tocolytics alone. Women in the progesterone and placebo groups had longer latency to delivery, lower rates of delivery within 7 days, and lower rates of PTB than controls. As a result, neonates of mothers in the progesterone and placebo groups had higher mean BW, lower composite morbidities, lower rates of NICU admission and shorter lengths of NICU stay compared to neonates of women in the control group.

The present results suggest, that the gel vehicle rather than the progesterone component was the factor that prevented PTB. Most likely, the acidic gel vehicle reinforced the biochemical barrier at the uterine cervix, which protected the pregnancy from pathogen invasion and uterine infection and thereby delayed PTB. A physiological *Lactobacillus*-dominated vaginal microbiome promotes an acidic low pH less than 4.5, which constitutes a biochemical barrier against ascending pathogens from the skin and bowel microbiota. This biochemical barrier protects the pregnancy from infection which is a known trigger of myometrial contractions and PTL. The physiological vaginal microbiome undergoes significant changes during pregnancy resulting in a more acidic lower pH. In contrast, alterations in the vaginal microbiome resulting in a higher pH are associated with PTB [7, 17]. The present results were in accordance with

reports on uterine infection due to ascending pathogen invasion as an ethiology behind 30–60 % of all early PTB [2]. The present findings were also in agreement with results showing that the gel base exerts anti-inflammatory effects, decreases the cervical collagen metabolizing enzyme MMP-13, and delays PTB [18].

Randomized trials on maintenance treatment with vaginal progesterone after the onset of PTL are warranted, as only a few trials on this topic have been published [19]. Two trials report longer latency to delivery after vaginal progesterone compared to no treatment [15, 20], one trial reports longer latency to delivery after progesterone compared to placebo [21], and one reports no differences after vaginal progesterone, intramuscular progestin 17OH-PC, or no treatment [22]. The discrepancies between the present results and previous ones could be explained by the different study designs. Participants in the present trial were included at mean 26 weeks in contrast to 31 weeks or more [15, 20 – 21] and 28 weeks or more [22] in previous trials. Spontaneous PTL was 2 or more uterine contractions per 10 min for more than 30 min resulting in a CL less than 25 mm without cervical dilatation determined by transvaginal ultrasound in the present trial and one of the previous trials [22], in contrast to cervical shortening and/or softening or dilatation [15], cervical softening, shortening at least by 50 % and dilatation less than 2 cm [20] or cervical dilatation and/or effacement [21] assessed by digital examination. Transvaginal ultrasound is recommended for CL determination in women with PTL, whereas the accuracy of digital assessment is questioned [13, 14]. Intravenous tocolysis in the present trial consisted of an oxytocin receptor antagonist or a β2–receptor agonist in contrast to magnesium sulfate in combination with ampicillin [15], a β2–receptor agonist [20], magnesium sulfate in combination with pethidine and ampicillin [21], an oxytocin receptor antagonist, a calcium blocker or a non-steroidal anti-inflammatory drug (NSAID) [22]. The maintenance treatment consisted of progesterone gel 90 mg in the present trial, in contrast to vaginal progesterone suppositories 400 mg [15] or 200 mg [20 – 22] in previous reports.

Different bioavailabilities of the progesterone preparations could have influenced the diverse results in the present trial and the previous ones. However, the clinical effects are similar when vaginal progesterone gel is compared to a progesterone suppository for luteal phase support in early pregnancy [23].

Strengths of this trial were the consistent inclusion and exclusion criteria, the transvaginal ultrasound CL determination, and that all data were retrieved from original electronic obstetric records at one hospital. Limitations were the lack of double blinded design and the slow inclusion of participants. It is possible also, that the inclusion and follow-up in the treatment groups reduced chronic psychosocial stress, which is a known risk factor of PTL, and thereby prevented PTB in these groups [24 – 25].

Conclusion

The present results showed, that maintenance treatment with vaginal progesterone gel and placebo were equally effective in preventing PTB among women with PTL. However, both progesterone and placebo prolonged pregnancy more effectively than intravenous tocolysis alone. We hypothesize, that the acidic

gel base reinforced the biochemical barrier at the uterine cervix, which counteracted ascending pathogen invasion and subsequent inflammation and thereby delayed PTB. The present results suggest, that non-hormonal agents that reinforce the biochemical cervical barrier can be useful for the prevention of PTB in clinical practice.

List Of Abbreviations

BW Birth weight; **CL** Cervical length; **IVH** Intraventricular hemorrage; **MMP** Matrix metalloproteinase enzyme; **NEC** Necrotizing Enterocolitis; **NICU** Neonatal Intensive Care Unit; **PTB** Preterm Birth, **PTL** Preterm Labor, **RDS** Respiratory Distress Syndrome; **ROP** Retinopathy of Prematurity.

Declarations

Ethical approval

Ethics approval was obtained from the Regional Ethics Board for Medical Sciences in Stockholm in September 2007, No 2007-311-31. The trial was registered at the European Union Drug Regulating Authorities Clinical Trials (EudraCT)**, that participates in the World Health Organization (WHO) International Clinical Trial Registry Platform in September 2007,** No 2007-003348-31, and was approved by the Swedish Medical Products Agency in May 2008, No 151:2008/30388. Ethics approval for the control group of women who were identified in retrospect was obtained from the Regional Ethics Board for Medical Sciences in Stockholm in April 2015, No 2014/255-31.

Consent for publication

The authors Giovanna Marchini, Tomislav Vladic and Ylva Vladic Stjernholm read and approved the manuscript.

Data availability

All data analyzed during this trial are included in this article and are available if requested.

Competing interests

The authors declare no competing interests.

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Author contributions

GM and YVS planned and designed the study and collected the data. GM, TV and YVS analyzed the data, wrote and approved the manuscript.

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Tables

Table 1. Patient characteristics.

Variable	Progesterone	Placebo	Control
	n = 29	n = 29	n = 29
Age, years (mean ± SD)	31 ± 4	29 ± 6	32 ± 5
BMI, kg/m^2 (mean ± SD)	24 ± 5	23 ± 3	24 ± 2
Primiparous, n (%)	12 (44)	16 (55)	16 (55)
GA, weeks ± d (mean)	26 ±12	26 ± 17	27 ± 17
CL, mm (mean ± SD)	11 ± 5	12 ± 5	14 ± 7
Tocolysis Atosiban/terbutaline, n (%)	23/4 (85/15)	26/3 (90/10)	26/3 (90/10)

Abbreviations: BMI = body mass index; CL = cervical length at start of treatment; GA = gestational age at start of treatment.

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Table 2. Maternal outcome.

Statistical methods Mann Whitney U-test, General linear model and One way ANOVA[1], and Chi[2]-test and Fisher´s exact test[2].

Variable	Progesterone n = 29	95% CI	Placebo n = 29	95% CI	p value PR *vs* PL	Control n = 29	95% CI	p value PR *vs* C	p value PL *vs* C
Latency, days (mean ± SD)	58 ± 34	(45 – 72)	64 ± 51	(45 – 93)	0.84[1]	2 ± 2	(1 – 3)	< 0.001[1]	< 0.001[1]
Delivery ≤ 7 d, n (%)	4 (14)		6 (21)		0.06[2]	29 (100)		< 0.001[1]	< 0.001[1]
PTB < 34 + 0 weeks, n (%)	9 (34)		11 (38)		0.32[2]	29 (100)		0.01[2]	0.02[2]
PTB < 37 + 0 weeks, n (%)	15 (52)		13 (45)		0.65[2]	29 (100)		0.06[2]	0.04[2]

Abbreviations: C = control; CI = confidence interval; Delivery < 7 d = delivery within 7 d after randomization; Latency = latency from randomization to childbirth; PTB = preterm birth; PL = placebo; PR = progesterone.

Table 3. Neonatal outcome.

Statistical methods Mann Whitney U-test and One way ANOVA[1]; Chi[2]-test and Fisher´s exact test[2].

Variable	Progesterone n = 29	95% CI	Placebo n = 29	95% CI	p value PR *vs* PL	Control n = 29	95 % CI	p value PR *vs* C	p value PL *vs* C
BW, g (mean ± SD)	2471 ± 1078	(1970 – 2839)	2452 ± 1054	(2052 – 2854)	0.84[1]	1023 ± 409	(844 – 1087)	< 0.001[1]	< 0.001[1]
Composite morbidity, n (%)	21 (72)		19 (65)		0.65[2]	57 (120)		< 0.001[2]	< 0.001[2]
Apgar < 7 at 5 min	3		2			9			
IVH	1		2			4			
NEC	2		1			2			
RDS	8		8			27			
Sepsis	3		4			8			
ROP	2		1			5			
Death	2		1			2			
NICU admission, n (%)	9 (31)		7 (24)		0.12[2]	29 (100)		< 0.001[1]	< 0.001[1]
NICU stay, days (mean ± SD)	10 ± 25	(2 – 21)	10 ± 21	(1 – 18)	0.59[1]	70 ± 40	(55 – 86)	< 0.001[1]	< 0.001[1]

Abbreviations: BW = birth weight; C = control; CI = confidence interval; Composite morbidity = Apgar < 7 at 5 min, IVH (Intraventricular Hemorrage), NEC (Necrotizing Enterocolitis), RDS (Respiratory Distress Syndrome), and sepsis ≤ 7 days, taken together with ROP (Retinopathy of Prematurity) and death during NICU stay; NICU = Neonatal Intensive Care Unit; PL = placebo; PR = progesterone.

Figures

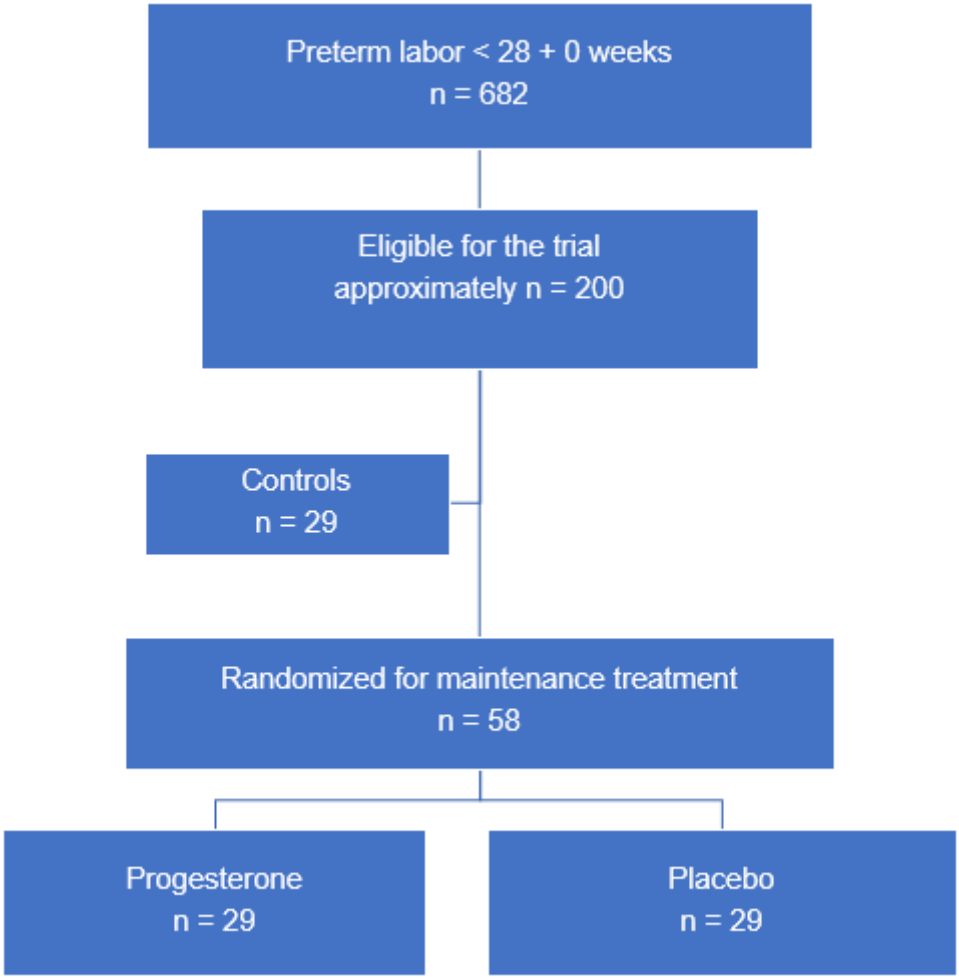

Figure 1

Inclusion of participants in 2009 — 18.

Supplementary Files

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- S2EudraCT2007.pdf