ORIGINAL ARTICLE

A Randomized Trial of Progesterone in Women with Recurrent Miscarriages

A. Coomarasamy, H. Williams, E. Truchanowicz, P.T. Seed, R. Small, S. Quenby,
P. Gupta, F. Dawood, Y.E.M. Koot, R. Bender Atik, K.W.M. Bloemenkamp,
R. Brady, A.L. Briley, R. Cavallaro, Y.C. Cheong, J.J. Chu, A. Eapen, A. Ewies,
A. Hoek, E.M. Kaaijk, C.A.M. Koks, T.-C. Li, M. MacLean, B.W. Mol, J. Moore,
J.A. Ross, L. Sharpe, J. Stewart, N. Vaithilingam, R.G. Farquharson, M.D. Kilby,
Y. Khalaf, M. Goddijn, L. Regan, and R. Rai

ABSTRACT

BACKGROUND

Progesterone is essential for the maintenance of pregnancy. However, whether progesterone supplementation in the first trimester of pregnancy would increase the rate of live births among women with a history of unexplained recurrent miscarriages is uncertain.

METHODS

We conducted a multicenter, double-blind, placebo-controlled, randomized trial to investigate whether treatment with progesterone would increase the rates of live births and newborn survival among women with unexplained recurrent miscarriage. We randomly assigned women with recurrent miscarriages to receive twice-daily vaginal suppositories containing either 400 mg of micronized progesterone or matched placebo from a time soon after a positive urinary pregnancy test (and no later than 6 weeks of gestation) through 12 weeks of gestation. The primary outcome was live birth after 24 weeks of gestation.

RESULTS

A total of 1568 women were assessed for eligibility, and 836 of these women who conceived naturally within 1 year and remained willing to participate in the trial were randomly assigned to receive either progesterone (404 women) or placebo (432 women). The follow-up rate for the primary outcome was 98.8% (826 of 836 women). In an intention-to-treat analysis, the rate of live births was 65.8% (262 of 398 women) in the progesterone group and 63.3% (271 of 428 women) in the placebo group (relative rate, 1.04; 95% confidence interval [CI], 0.94 to 1.15; rate difference, 2.5 percentage points; 95% CI, −4.0 to 9.0). There were no significant between-group differences in the rate of adverse events.

CONCLUSIONS

Progesterone therapy in the first trimester of pregnancy did not result in a significantly higher rate of live births among women with a history of unexplained recurrent miscarriages. (Funded by the United Kingdom National Institute of Health Research; PROMISE Current Controlled Trials number, ISRCTN92644181.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Coomarasamy at a.coomarasamy@bham .ac.uk.

ECURRENT MISCARRIAGE, DEFINED AS the loss of three or more pregnancies, affects approximately 1% of couples who attempt to have a child.[1] Even after comprehensive investigations, a cause for recurrent miscarriage is identified in less than half of these couples.[1,2] Unexplained recurrent miscarriage is associated with substantial adverse clinical and psychological consequences for the women and their families. Various therapeutic strategies to increase the rate of live births among these women have been evaluated, but no effective treatment has been identified.

Progesterone is essential to achieve and maintain a healthy pregnancy. It is secreted naturally by the corpus luteum during the second half of the menstrual cycle and by the corpus luteum and placenta during early pregnancy. Progesterone prepares the endometrium for implantation of the embryo. If implantation occurs, the corpus luteum continues to produce progesterone, but between 8 and 12 weeks of gestation, the placenta takes over this role and maintains the pregnancy thereafter.[3]

The physiological importance of progesterone in early pregnancy has prompted the performance of several trials to evaluate the effect of progesterone supplementation in the first trimester of pregnancy among women with a history of recurrent miscarriages. A Cochrane review of four small trials showed a significantly lower risk of miscarriages among women who received progesterone than among those who received placebo or no treatment (odds ratio, 0.39; 95% confidence interval [CI], 0.21 to 0.72), but the quality of the four trials was considered to be poor.[4] We designed this multicenter, randomized, placebo-controlled trial (Progesterone in Recurrent Miscarriages [PROMISE]) to investigate whether treatment with progesterone would increase the rates of live births and newborn survival among women with unexplained recurrent miscarriage.

METHODS

STUDY OVERSIGHT

The PROMISE trial was approved by the United Kingdom Medicines and Healthcare Products Regulatory Authority, the National Research Ethics Service, and the research and development department at each participating hospital. Progesterone and placebo were manufactured and supplied by Besins Healthcare. This company had no role in the design of the study; the collection, analysis, or interpretation of the data; or the writing of the report. All the authors were involved in the collection, analysis, and interpretation of the data; the writing and critical review of the manuscript; and the decision to submit the manuscript for publication. Study oversight and monitoring were provided by a trial steering committee and by an independent data and safety monitoring committee. The first, second, and last authors vouch for the accuracy of the data and analyses and for the fidelity of the study to the protocol (available with the full text of this article at NEJM.org).

STUDY PARTICIPANTS

The participants in the PROMISE trial were recruited from hospitals located across the United Kingdom (36 sites) and in the Netherlands (9 sites). Women were eligible for enrollment in the study if they were 18 to 39 years of age and were actively trying to conceive naturally after having received a diagnosis of unexplained recurrent miscarriage (defined as three or more consecutive or nonconsecutive losses of pregnancy in the first trimester). Age criteria were applied for participation in the trial because the likelihood of miscarriages due to random chromosomal aberrations increases with advancing age,[1,5] and progesterone therapy would probably not prevent such miscarriages.

All participants gave written informed consent. Participants were excluded from randomization if they were unable to conceive naturally within 1 year after recruitment; had the antiphospholipid syndrome or other recognized thrombophilic conditions; had uterine cavity abnormalities (as assessed with the use of ultrasonography, hysterosonography, hysterosalpingogram, or hysteroscopy), an abnormal parental karyotype, or other identifiable cause of recurrent miscarriage such as diabetes, thyroid disease, or systemic lupus erythematosus (tests were initiated only if clinically indicated); were currently receiving heparin therapy; or had contraindications to progesterone use.

STUDY DESIGN AND DRUG REGIMEN

Participants were randomly assigned in a 1:1 ratio to receive vaginal suppositories containing either 400 mg of micronized progesterone (Utrogestan, Besins Healthcare) twice daily or matched pla-

cebo from a time soon after receiving positive results on a urinary pregnancy test (and no later than 6 weeks of gestation) through 12 completed weeks of gestation (or earlier if an ectopic pregnancy was diagnosed or miscarriage occurred before 12 weeks). Computerized randomization was performed centrally through a secure Internet facility with the use of minimization to balance the study-group assignments according to the number of previous miscarriages (3 or ≥4), maternal age (≤35 or >35 years), presence or absence of polycystic ovaries, and body-mass index (BMI [the weight in kilograms divided by the square of the height in meters], ≤30 or >30). The appearance, route, and timing of administration of the study drugs were identical in the placebo and progesterone groups. Participants, physicians, and trial nurses were unaware of the study-group assignments throughout the trial.

OUTCOME MEASURES

The primary outcome measure was live birth after 24 completed weeks of gestation. Secondary outcomes included clinical pregnancy (presence of at least a gestational sac) at 6 to 8 weeks, ongoing pregnancy with fetal heart activity at 12 weeks, miscarriage (pregnancy loss before 24 weeks of gestation), the week of gestation at delivery, survival at 28 days of neonatal life, and congenital abnormalities (specifically genital anomalies, because there has been concern about a possible increased risk of hypospadias with the use of certain progesterone analogues[6]). Exploratory outcomes included obstetrical conditions such as preeclampsia, small size for gestational age (<10th percentile for birth weight), preterm prelabor rupture of membranes, antepartum hemorrhage, and mode of delivery, as well as neonatal variables such as birth weight, arterial and venous pH, Apgar scores, and need for ventilation support.

STATISTICAL ANALYSIS

We calculated that we would need to assign 376 women to each study group for the study to have 80% power to detect a minimally important absolute difference of 10 percentage points between the progesterone group and the placebo group with respect to the rate of live births after 24 weeks (from 60% to 70%; odds ratio, 1.56), at an alpha level of 0.05. We planned to include 790 women in the study to account for a 5% rate of loss to follow-up.

Categorical baseline data were reported as absolute numbers and percentages. Normally distributed continuous variables were summarized as means with standard deviations, and nonnormally distributed continuous variables were reported as medians with interquartile ranges. The analyses were performed according to the intention-to-treat principle. Binary regression with a log-link function was used to determine the relative rates for the primary outcome and other binary outcomes, with adjustment for the minimization variables. Continuous outcomes were analyzed as mean differences or ratios, as appropriate.

The primary end point was analyzed with the use of multivariate logistic regression in three prespecified subgroups defined according to maternal age (≤35 vs. >35 years), number of previous miscarriages (3 vs. ≥4), and presence or absence of polycystic ovaries, and in three additional post hoc subgroups defined according to gestation at treatment start (<5 weeks 0 days vs. ≥5 weeks 0 days), BMI (≤30 vs. >30), and country (United Kingdom vs. the Netherlands). In each subgroup analysis, we first used a chi-square test for interaction to determine whether the effects of progesterone and placebo differed in any of the subgroups.

Interim analyses of principal safety and effectiveness end points were performed on behalf of the data and safety monitoring committee on two occasions. Because these analyses were performed with the use of the Peto principle,[7] no adjustment was made in the final P values to determine significance.

RESULTS

STUDY PARTICIPANTS

A total of 1568 women were assessed for eligibility for the PROMISE trial from June 23, 2010, through October 23, 2013, and 836 of these women who conceived naturally within 1 year and remained willing to participate in the trial were randomly assigned to receive either progesterone (404 women) or placebo (432 women) (Fig. 1). The follow-up rate for the primary outcome was 98.8% (826 of 836 women). The baseline characteristics were similar in the two study groups (Table 1).

OUTCOMES

The rate of live births after 24 weeks of gestation was 65.8% (262 of 398 pregnancies) in the pro-

Figure 1. Enrollment, Randomization, Follow-up, and Analysis.
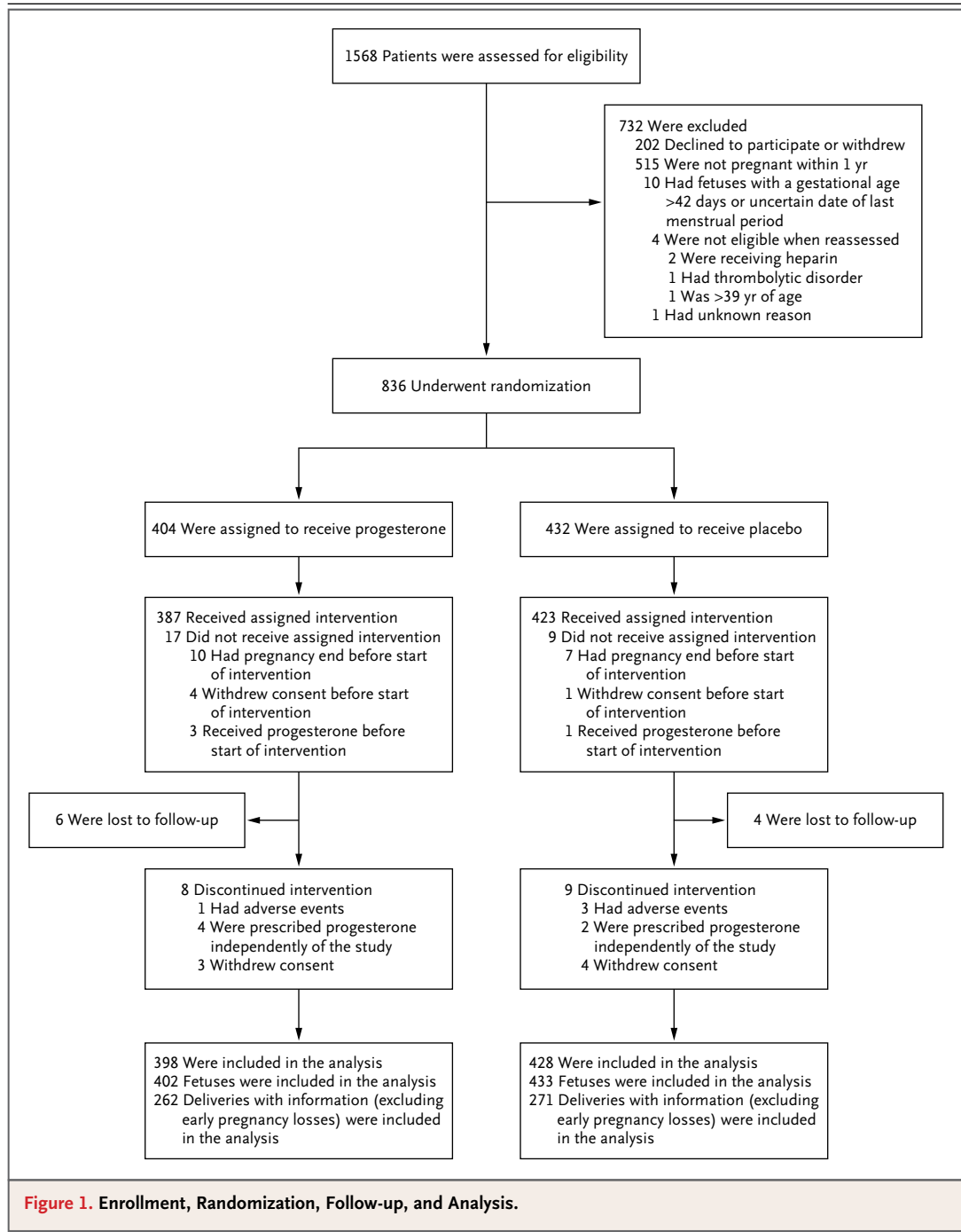
gesterone group, as compared with 63.3% (271 of 428 pregnancies) in the placebo group (relative rate, 1.04; 95% CI, 0.94 to 1.15; absolute rate difference, 2.5 percentage points; 95% CI, −4.0 to 9.0).

There were no significant between-group differences in the rates of clinical pregnancy (at 6 to 8 weeks), ongoing pregnancy (at 12 weeks),

ectopic pregnancy, miscarriage, stillbirth, and neonatal outcomes, as well as in the median gestational age at miscarriage (Table 2). A total of 533 pregnancies in the two study groups progressed to live birth after 24 weeks; the babies were delivered before 34 weeks in 10 of 262 pregnancies (3.8%) in the progesterone group

Table 1. Characteristics of the Participants at Baseline.*

Characteristic	Progesterone (N = 404)	Placebo (N = 432)
Maternal age — yr†		
Median	32.9	32.5
Interquartile range	29.3–36.3	28.9–35.9
Maternal BMI	25.5±5.1	25.3±5.1
Maternal BMI >30.0 — no./total no. (%)	63/404 (15.6)	65/432 (15.0)
Maternal race — no./total no. (%)‡		
White	316/399 (79.2)	366/424 (86.3)
Black	16/399 (4.0)	19/424 (4.5)
Asian	39/399 (9.8)	29/424 (6.8)
Other, including mixed race	28/399 (7.0)	10/424 (2.4)
Maternal smoking — no./total no. (%)		
Nonsmoker	339/404 (83.9)	363/432 (84.0)
<10 cigarettes/day	28/404 (6.9)	34/432 (7.9)
10 to 19 cigarettes/day	31/404 (7.7)	27/432 (6.2)
≥20 cigarettes/day	6/404 (1.5)	8/432 (1.9)
Alcohol use — no./total no. (%)§		
None	229/404 (56.7)	260/432 (60.2)
≤3 units/day	92/404 (22.8)	89/432 (20.6)
>3 to ≤20 units/day	82/404 (20.3)	83/432 (19.2)
>20 units/day	1/404 (0.2)	0/432
Parity		
Previous live birth — no./total no. (%)	167/404 (41.3)	179/432 (41.4)
≥4 previous miscarriages — no./total no. (%)	183/404 (45.3)	192/432 (44.4)
Previous pregnancy losses — no.		
Median	3.0	3.0
Interquartile range	3.0–5.0	3.0–4.0
Clinical risk factors — no./total no. (%)		
Polycystic ovaries	30/404 (7.4)	28/432 (6.5)
Fibroids	15/404 (3.7)	14/432 (3.2)
Large-loop excision of the cervical transformation zone	10/404 (2.5)	19/432 (4.4)
Family history of recurrent miscarriages	55/368 (14.9)	63/391 (16.1)
Concurrent medications — no./total no. (%)		
Metformin	4/404 (1.0)	2/432 (0.5)
Aspirin	38/404 (9.4)	37/432 (8.6)

* Plus–minus values are means ±SD. The baseline data (age, body-mass index [BMI; the weight in kilograms divided by the square of the height in meters], maternal race, smoking status, and parity) of the participants were similar (without significant differences) in the two study groups.
† Listed is the maternal age at the time of randomization.
‡ Race was self-reported.
§ One unit is 10 g of pure alcohol.

and in 10 of 271 pregnancies (3.7%) in the placebo group (relative risk, 1.03; 95% CI, 0.44 to 2.45). The distributions of gestational age at the time of live-birth delivery were similar in the two study groups (Fig. 2).

The frequency of adverse events did not differ

Table 2. Primary Outcome and Secondary Outcomes.

Outcome	Progesterone	Placebo	Relative Risk (95% CI)	P Value
	no./total no. (%)			
Pregnancy outcomes				
Clinical pregnancy at 6 to 8 weeks	326/398 (81.9)	334/428 (78.0)	1.05 (0.98–1.12)	0.16
Ongoing pregnancy at 12 weeks	267/398 (67.1)	277/428 (64.7)	1.04 (0.94–1.14)	0.47
Ectopic pregnancy	6/398 (1.5)	7/428 (1.6)	0.92 (0.31–2.72)	0.88
Miscarriage*	128/398 (32.2)	143/428 (33.4)	0.96 (0.79–1.17)	0.70
Stillbirth	1/398 (0.3)	2/428 (0.5)	0.54 (0.05–5.92)	0.61
Live birth after 24 weeks 0 days of gestation†	262/398 (65.8)	271/428 (63.3)	1.04 (0.94–1.15)	0.45
Twin live births after 24 weeks 0 days of gestation†	4/398 (1.0)	5/428 (1.2)	0.86 (0.23–3.18)	0.82
Gestation outcomes among women with live births				
Live birth before 28 weeks 0 days of gestation	1/262 (0.4)	1/271 (0.4)	1.03 (0.06–16.49)	0.98
Live birth before 34 weeks 0 days of gestation	10/262 (3.8)	10/271 (3.7)	1.03 (0.44–2.45)	0.94
Live birth before 37 weeks 0 days of gestation	27/262 (10.3)	25/271 (9.2)	1.12 (0.67–1.87)	0.68
Neonatal outcomes‡				
Any congenital anomaly	8/266 (3.0)	11/276 (4.0)	0.75 (0.31–1.85)	0.54
Genital congenital anomaly	1/266 (0.4)	1/276 (0.4)	1.04 (0.07–16.50)	0.98
Newborn survival to 28 days†	260/261 (99.6)	269/269 (100)	1.00 (0.99–1.00)	0.32

* The median gestational age at miscarriage was 7.3 weeks (interquartile range, 6.0 to 8.7) in the progesterone group and 7.1 weeks (interquartile range, 6.0 to 8.5) in the placebo group (relative risk, 0.0; 95% CI, –0.6 to 0.4; P=0.87).
† The end point is listed per trial participant.
‡ The end point is listed per neonate.

significantly between the progesterone group and the placebo group (Table S1 in the Supplementary Appendix, available at NEJM.org). Neonatal congenital anomalies were observed in 3.5% of the babies (8 of 266 babies [3.0%] in the progesterone group, as compared with 11 of 276 babies [4.0%] in the placebo group; relative risk, 0.75; 95% CI, 0.31 to 1.85). A urogenital abnormality was observed in 1 baby in each group (a hypospadias in the progesterone group and a urachal cyst in the placebo group).

No evidence of effect modification was identified in the prespecified subgroups (defined according to maternal age, number of previous miscarriages, and presence or absence of polycystic ovaries) or in the post hoc subgroups (defined according to gestation at the start of treatment, BMI, and country) (Table S2 in the Supplementary Appendix). In exploratory analyses, we found no significant differences between the two study groups in the rates of obstetrical or neonatal adverse outcomes (Table S3 in the Supplementary Appendix).

DISCUSSION

This large multicenter, randomized, placebo-controlled trial showed that progesterone therapy in the first trimester of pregnancy did not result in a significant increase in the rate of live births among women with a history of unexplained recurrent miscarriages. Our results do not support earlier findings of a Cochrane analysis that suggested a benefit of progesterone therapy in the first trimester of pregnancy.[4] The Cochrane analysis pooled the results from four small trials that had substantive methodologic limitations[8-11]; none of the trials specified the method of concealment of study-group assignments, and only two trials used a placebo for comparison. A more recent double-blind, placebo-controlled, randomized trial of oral dydrogesterone (given from the time that pregnancy was confirmed until 20 weeks of gestation) among 360 women with a history of recurrent miscarriages also showed a benefit of progesterone in reducing a subsequent risk of miscarriage[12]

(relative risk of miscarriage with placebo, as compared with dydrogesterone, 2.4; 95% CI, 1.3 to 5.9); there were no significant between-group differences in the rates of preterm birth, cesarean deliveries, or babies with low birth weights. None of the previous trials assessed rates of live births.

Several limitations of our study should be considered. We studied a vaginal preparation of progesterone, at a dose of 400 mg twice daily, and it is possible that the results with this regimen are not generalizable to patients receiving other doses and preparations. However, we chose this route to deliver a greater proportion of the drug to the biologically relevant site (i.e., the uterus),[13,14] and the dose used (400 mg twice daily) represents a dose at the top end of the therapeutic window.[15] Some researchers have suggested that intramuscular preparations of progesterone may provide greater therapeutic benefit than vaginal preparations; however, data are lacking to support this contention, and previous trials of alternative progesterone preparations (including intramuscular progesterone) have shown varying results.[8,9] Furthermore, previous studies have shown the efficacy of vaginal progesterone in lowering the risk of preterm birth.[16-18]

We initiated progesterone treatment after pregnancy was confirmed, and thus our study cannot address whether progesterone supplementation could be more effective in reducing the risk of miscarriage if administered during the luteal phase of the cycle, before the confirmation of pregnancy.[19-22] We discontinued progesterone at 12 weeks of gestation but consider it unlikely that therapy beyond this time would result in better outcomes; it is well documented that corpus luteal function is replaced by placental production of progesterone before the end of the first trimester.[3] Moreover, among PROMISE participants who had a miscarriage, the median gestation was less than 8 weeks (7.3 weeks in the progesterone group and 7.1 weeks in the placebo group).

We found no increase in the risk of congenital anomalies among offspring of women treated with progesterone, although the study was not powered for such rare outcomes. Nonetheless, this finding is reassuring because progesterone therapy is commonly used as part of assisted-conception treatment.

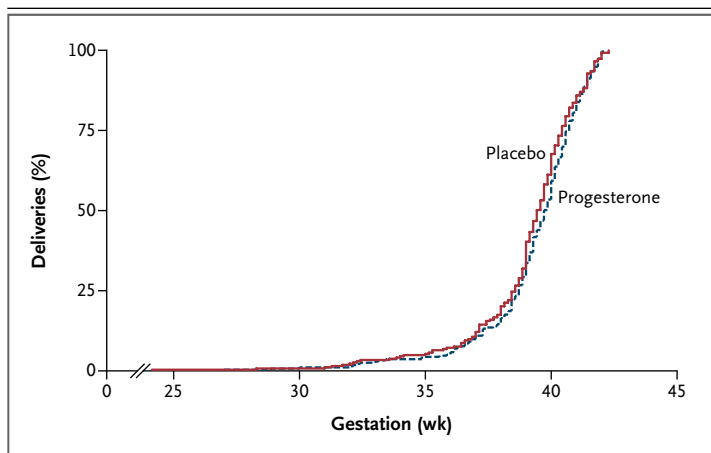In conclusion, our trial showed no significant

Figure 2. Distribution of Gestational Age According to Study Group Assignment.
Only pregnancies that continued beyond 24 weeks are shown. The hazard ratio for miscarriage in the progesterone group, as compared with the placebo group, was 1.04 (95% CI, 0.91 to 1.19).

increase in the rate of live births with the use of vaginal progesterone in the first trimester of pregnancy among women with recurrent miscarriages. Our results do not support the earlier findings of a Cochrane review[4] that suggested a benefit of progesterone therapy in the first trimester among women with recurrent miscarriages.

APPENDIX

The authors' full names and academic degrees are as follows: Arri Coomarasamy, M.B., Ch.B., M.D., Helen Williams, B.Sc., Ewa Truchanowicz, Ph.D., Paul T. Seed, M.Sc., Rachel Small, R.G.N., R.M., Siobhan Quenby, M.D., Pratima Gupta, M.D., Feroza Dawood, M.B., Ch.B., M.D., Yvonne E.M. Koot, M.D., Ruth Bender Atik, B.A., Kitty W.M. Bloemenkamp, M.D., Ph.D., Rebecca Brady, R.N.Dip., M.Sc., T.N.Dip., Annette L. Briley, Ph.D., Rebecca Cavallaro, R.M., R.N., M.Mid., Ying C. Cheong, M.B., Ch.B., M.D., Justin J. Chu, M.D., Abey Eapen, M.D., Ayman Ewies, M.B., Ch.B., M.D., Annemieke Hoek, M.D., Ph.D., Eugenie M. Kaaijk, M.D., Carolien A.M. Koks, M.D., Tin-Chiu Li, M.D., Marjory MacLean, M.D., Ben W. Mol, M.D., Ph.D., Judith Moore, M.R.C.O.G., Jackie A. Ross, M.B., B.S., Lisa Sharpe, R.M.Dip., Jane Stewart, M.B., Ch.B., M.D., Nirmala Vaithilingam, M.D., Roy G. Farquharson, M.D., Mark D. Kilby, M.B., B.S., M.D., Yacoub Khalaf, M.B., B.Ch., M.D., Mariette Goddijn, M.D., Ph.D., Lesley Regan, M.D., and Rajendra Rai, M.D.

The authors' affiliations are as follows: the College of Medical and Dental Sciences, University of Birmingham (A.C., H.W., E.T., J.J.C., A. Eapen, M.D.K.), Heart of England NHS Foundation Trust (R.S., P.G.), and Sandwell and West Birmingham Hospitals NHS Teaching Trust (A. Ewies), Birmingham, King's College London and King's Health Partners at St. Thomas' Hospital (P.T.S.), Women's Health Research Center, Imperial College at St. Mary's Hospital Campus (R.B., R.C., L.S., L.R., R.R.), King's Health Partners at St. Thomas' Hospital (A.L.B.), King's College Hospital NHS Foundation Trust (J.A.R.), and Assisted Conception Unit, Guy's and St. Thomas' Foundation Trust (Y.K.), London, Biomedical Research Unit in Reproductive Health, University of Warwick, Warwick (S.Q.), Liverpool Women's NHS Foundation Trust (F.D., R.G.F.), Liverpool, The Miscarriage Association, Wakefield (R.B.A.), University of Southampton Faculty of Medicine, Princess Anne Hospital, Southampton (Y.C.C.), Royal Hallamshire Hospital, Sheffield (T.-C.L.), Ayrshire Maternity Unit, University Hospital of Crosshouse, Kilmarnock (M.M.), Nottingham University Hospitals NHS Trust, Nottingham (J.M.), Newcastle Hospitals NHS Foundation Trust, Newcastle upon Tyne (J.S.), and Portsmouth Hospitals NHS Trust, Portsmouth (N.V.) — all in the United Kingdom; the Department of Reproductive Medicine, University Medical Center Utrecht, Utrecht (Y.E.M.K.), the Department of Obstetrics, Leiden University Medical Center, Leiden (K.W.M.B.), the Department of Reproductive Medicine and Gynecology, University of Groningen, Groningen (A.H.), the Department of Obstetrics and Gynecology, Onze Lieve Vrouwe Gasthuis (E.M.K.), and Center for Reproductive Medicine, Department of Obstetrics and Gynecology, Academic Medical Center (M.G.), Amsterdam, and the Department of Obstetrics and Gynecology, Maxima Medical Center Veldhoven, Veldhoven (C.A.M.K.) — all in the Netherlands; and the Robinson Institute, School of Pediatrics and Reproductive Health, University of Adelaide, Adelaide, SA, Australia (B.W.M.).

REFERENCES

1. Rai R, Regan L. Recurrent miscarriage. Lancet 2006;368:601-11.
2. Practice Committee of the American Society for Reproductive Medicine. Evaluation and treatment of recurrent pregnancy loss: a committee opinion. Fertil Steril 2012;98:1103-11.
3. Malassiné A, Frendo JL, Evain-Brion D. A comparison of placental development and endocrine functions between the human and mouse model. Hum Reprod Update 2003;9:531-9.
4. Haas DM, Ramsey PS. Progestogen for preventing miscarriage. Cochrane Database Syst Rev 2013;10:CD003511.
5. Stephenson MD, Awartani KA, Robinson WP. Cytogenetic analysis of miscarriages from couples with recurrent miscarriage: a case-control study. Hum Reprod 2002;17:446-51.
6. Carmichael SL, Shaw GM, Laurent C, Croughan MS, Olney RS, Lammer EJ. Maternal progestin intake and risk of hypospadias. Arch Pediatr Adolesc Med 2005;159:957-62.
7. Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I: introduction and design. Br J Cancer 1976;34:585-612.
8. Swyer GI, Daley D. Progesterone implantation in habitual abortion. Br Med J 1953;1:1073-7.

9. Levine L. Habitual abortion: a controlled study of progestational therapy. West J Surg Obs Gynecol 1964;72:30-6.
10. Goldzieher JW. Double-blind trial of a progestin in habitual abortion. JAMA 1964;188:651-4.
11. El-Zibdeh MY. Dydrogesterone in the reduction of recurrent spontaneous abortion. J Steroid Biochem Mol Biol 2005;97:431-4.
12. Kumar A, Begum N, Prasad S, Aggarwal S, Sharma S. Oral dydrogesterone treatment during early pregnancy to prevent recurrent pregnancy loss and its role in modulation of cytokine production: a double-blind, randomized, parallel, placebo-controlled trial. Fertil Steril 2014; 102(5):1357.e3-1363.e3.
13. Bulletti C, de Ziegler D, Flamigni C, et al. Targeted drug delivery in gynaecology: the first uterine pass effect. Hum Reprod 1997;12:1073-9.
14. Cicinelli E, Cignarelli M, Sabatelli S, et al. Plasma concentrations of progesterone are higher in the uterine artery than in the radial artery after vaginal administration of micronized progesterone in an oil-based solution to postmenopausal women. Fertil Steril 1998;69:471-3.
15. Nosarka S, Kruger T, Siebert I, Grove D. Luteal phase support in in vitro fertilization: meta-analysis of randomized trials. Gynecol Obs Invest 2005;60:67-74.
16. Coomarasamy A, Truchanowicz EG,

Rai R. Does first trimester progesterone prophylaxis increase the live birth rate in women with unexplained recurrent miscarriages? BMJ 2011;342:d1914.
17. Da Fonseca EB, Bittar RE, Carvalho MH, Zugaib M. Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: a randomized placebo-controlled double-blind study. Am J Obstet Gynecol 2003;188:419-24.
18. Fonseca EB, Celik E, Parra M, Singh M, Nicolaides KH. Progesterone and the risk of preterm birth among women with a short cervix. N Engl J Med 2007;357:462-9.
19. Daya S. Efficacy of progesterone support for pregnancy in women with recurrent miscarriage: a meta-analysis of controlled trials. Br J Obstet Gynaecol 1989; 96:275-80.
20. Ozlü T, Güngör AC, Dönmez ME, Duran B. Use of progestogens in pregnant and infertile patients. Arch Gynecol Obstet 2012;286:495-503.
21. Sonntag B, Ludwig M. An integrated view on the luteal phase: diagnosis and treatment in subfertility. Clin Endocrinol (Oxf) 2012;77:500-7.
22. Shah D, Nagarajan N. Luteal insufficiency in first trimester. Indian J Endocrinol Metab 2013;17:44-9.
Copyright © 2015 Massachusetts Medical Society.