

NUOVI PRESIDI NELLA PREVENZIONE DELL'ABORTO SPONTANEO E DEL PARTO PRETERMINE

DOTT.SSA SILVIA VISENTIN

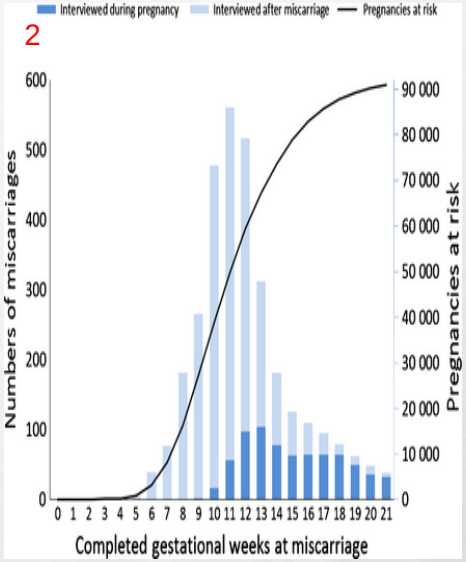
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Impact of the problem

Miscarriage is the spontaneous loss of a previable pregnancy. Previability refers to a fetus weighing <500g or to a gestational age (GA) < 20 weeks[1]

Miscarriage is the most common complication of early pregnancy[2]

- **30-40% of all conceptions end in miscarriage**
- **10-15% of clinically recognized pregnancies end at <20 weeks' GA**
- **25% risk in women younger than age 35, 45% risk in those older than age 40**
- **Other recognised risk factors are smoking, alcohol and illicit drug use, NSAID use, fever, caffeine and low folate levels.**



1. Prevenzione dell'aborto spontaneo

[1] The Johns Hopkins Manual of Gynecology and Obstetrics, 4ª ed., Lippincott Williams & Wilkins, 2012, pp. 438–439, ISBN 978-1-4511-4801-5.

[2] NICE Clinical Guidelines, No. 154. Royal College of Obstetricians and Gynaecologists. Archived from the original on October 20, 2013. Retrieved July 4, 2013.

[3] Feodor Nilsson, S, Pk Andersen2014. *"Risk Factors for Miscarriage from a Prevention Perspective: a Nationwide Follow-up Study."* BJOG: An International Journal of Obstetrics & Gynaecology 121 (11): 1375–85.

How do health care providers diagnose pregnancy loss or miscarriage?



Symptoms of miscarriage include:

- ✓ **Crampy abdominal pain**
- ✓ **Back pain**
- ✓ **Bleeding**
- ✓ **Light spotting**

For diagnosis

- a blood test to check for the level of βhCG
- an internal pelvic examination to determine if her cervix is dilated or thinned, which can be a sign of a miscarriage;
- an ultrasound test so that her health care provider can observe the pregnancy and the maternal reproductive organs, such as the uterus and placenta.[1]

If a woman has had more than one miscarriage, she may choose to have blood tests performed to check for chromosome abnormalities or hormone problems, or to detect immune system disorders that may interfere with a healthy pregnancy.[2]

1 Snell, B. J. (2009). *Assessment and management of bleeding in the first trimester of pregnancy*. Journal of Midwifery & Women's Health, 54(6), 483-491. doi:10.1016/j.jmwh.2009.08.007

2 Branch, D. W., Gibson, M., & Silver, R. M. (2010). *Clinical practice. recurrent miscarriage*. The New England Journal of Medicine, 363(18), 1740-1747. doi:10.1056/NEJMcp1005330

IS THERE A CURE FOR MISCARRIAGE?

IN MANY CASES, A WOMAN CAN DO LITTLE TO PREVENT A MISCARRIAGE

- Having pre-conception and prenatal care is the best prevention available for all complications associated with pregnancy.
- Miscarriages caused by systemic disease often can be prevented by detection and treatment of the disease before pregnancy occurs.
- A woman also can decrease her risk of miscarriage by avoiding environmental hazards, such as infectious diseases, X-rays, drugs and alcohol, and high levels of caffeine.



PubMed Health A.D.A.M. Medical Encyclopedia. (2010, November 21). Miscarriage. Retrieved May 21, 2012, from http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0002458/

Non-modifiable risk factors

Preventing a miscarriage in subsequent pregnancies may be enhanced with assessments of:

- Immune status
- Chemical and occupational exposures
- Anatomical defects
- Intercurrent diseases
- Polycystic ovary disease
- Previous exposure to Chemotherapy
- Previous exposure to Radiation
- Medications
- Surgical history
- Endocrine disorders
- Genetic abnormalities

Modifiable risk factors

Maintaining a healthy weight and good pre-natal care can reduce the risk of miscarriage. Some risk factors can be minimized by avoiding the following:

- Smoking
- Cocaine use
- Alcohol
- Poor nutrition
- Occupational exposure to agents that can cause miscarriage
- Medications associated with miscarriage
- Drug abuse

PubMed Health A.D.A.M. Medical Encyclopedia. (2010, November 21). Miscarriage. Retrieved May 21, 2012, from http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0002458/

FOLATE SUPPLEMENTS: ACTUALLY A GOOD IDEA

Obstet Gynecol. Author manuscript; available in PMC 2015 Jul 1.
PMCID: PMC4086728
Published in final edited form as:
NIHMSID: NIHMS592234
Obstet Gynecol. 2014 Jul; 124(1): 23–31.
doi: 10.1097/AOG.0000000000000343

Maternal Prepregnancy Folate Intake and Risk of Spontaneous Abortion and Stillbirth

Audrey J. Gaskins, Sc.D.,[1,2] Janet W. Rich-Edwards, Sc.D.,[2,7,8] Russ Hauser, M.D., Sc.D.,[2,3] Paige L. Williams, Ph.D.,[4] Matthew W. Gillman, M.D., S.M.,[1,5] Elizabeth S. Ginsburg, M.D.,[6] Stacey A. Missmer, Sc.D.,[2,6,7] and Jorge E. Chavarro, M.D., Sc.D.[1,2,7]

Author information ▶ Copyright and License information ▶

- Among the 11,072 women, 15,950 pregnancies were reported of which 2,756 ended in spontaneous abortion and 120 ended in stillbirth.
- Compared to women without supplemental folate intake those in the highest category (>730µg/day) had a RR of spontaneous abortion of 0.80
- The association of pre-pregnancy supplemental folate with risk of spontaneous abortion was consistent across gestational period of loss. A similar inverse trend was observed with the risk of stillbirth, which fell short of conventional significance

- Higher intake of folate from supplements was associated with reduced risk of spontaneous abortion. Women at risk of pregnancy should use supplemental folate for neural tube defect prevention and because it may decrease the risk of spontaneous abortion



VITAMINES SUPPLEMENTS: NOT PROVEN EFFICACY

Cochrane Database Syst Rev. 2016 May 6;(5):CD004073. doi: 10.1002/14651858.CD004073.pub4.

Vitamin supplementation for preventing miscarriage.

Balogun OO[1], da Silva Lopes K, Ota E, Takemoto Y, Rumbold A, Takegata M, Mori R.



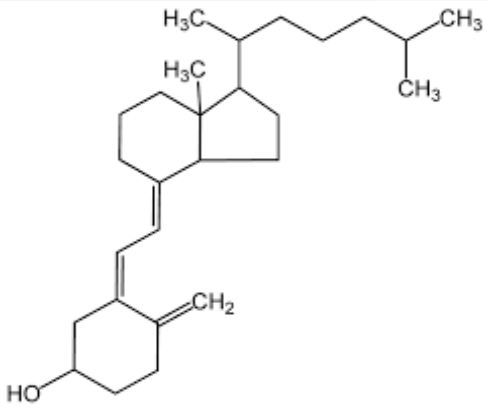
A total of 40 trials, involving 276,820 women and 278,413 pregnancies were included.

- **Vitamin C, Vitamin E, Vitamin A and Multivitamin supplements were studied and no evidence of differences in the risk of total fetal loss or miscarriage between women receiving any other combination compared with was found.**

AUTHORS' CONCLUSIONS: Taking any vitamin supplements prior to pregnancy or in early pregnancy does not prevent women experiencing miscarriage. However, evidence showed that women receiving multivitamins plus iron and folic acid had reduced risk for stillbirth. There is insufficient evidence to examine the effects of different combinations of vitamins on miscarriage and miscarriage-related outcomes.

However, many studies have been carried on the crucial role of Vitamine D

Vitamine D



1

Vitamin D insufficiency is associated with increased risk of first-trimester miscarriage in the Odense Child Cohort[1,2]

Conclusions: We found an association between 25(OH)D and first-trimester miscarriages, suggesting vitamin D as a modifiable risk factor for miscarriage. To test this hypothesis, randomized controlled trials should investigate the possible effect of vitamin D supplementation to increase 25(OH)D concentrations in early pregnancy, or before conception, to decrease risk of miscarriage. This trial was registered at clinicaltrials.gov as NCT02434900.

2

Humoral and cellular autoimmunity in women with recurrent pregnancy losses and repeated implantation failures: A possible role of vitamin D.

3

Vitamin D Deficiency in Early Pregnancy

Shannon K. Flood-Nichols,[1,*] Deborah Tinnemore,[2] Raywin R. Huang,[2] Peter G. Napolitano,[1] and Danielle L. Ippolito[2]

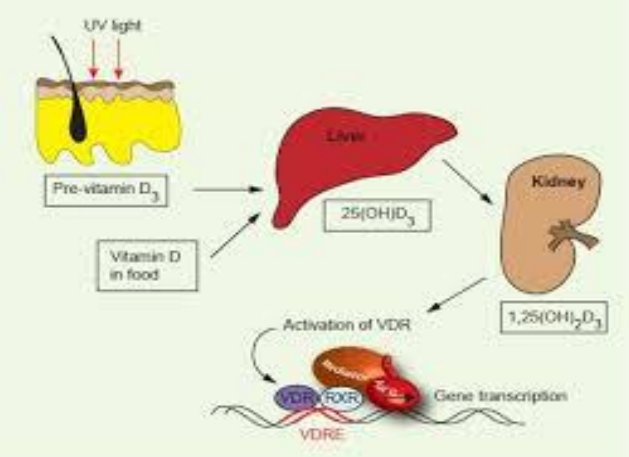
Ana Claudia Zenclussen, Academic Editor

[1]Andersen, Louise B., et al. 2015. "*Vitamin D Insufficiency Is Associated with Increased Risk of First-trimester Miscarriage in the Odense Child Cohort*." The American Journal of Clinical Nutrition 102 (3): 633–38. doi:10.3945/ajcn.114.103655.

[2]Kwak-Kim, Joanne, Annie Skariah,2016. *"Humoral and Cellular Autoimmunity in Women with Recurrent Pregnancy Losses and Repeated Implantation Failures: A Possible Role of Vitamin D."* Autoimmunity Reviews 15 (10): 943–47. doi:10.1016/j.autrev.2016.07.015.

[3]Flood-Nichols, Shannon K 2015. *"Vitamin D Deficiency in Early Pregnancy."* PLOS ONE 10 (4): e0123763. doi:10.1371/journal.pone.0123763.

VITAMINE D



IT SEEMS TO REGULATE THE CYTOKINE PATHWAYS IN THE ENDOMETRIUM..

1

Vitamin D deficiency may be a risk factor for recurrent pregnancy losses by increasing cellular immunity and autoimmunity FREE

2

Effects of 1,25(OH)2 Vitamin D3 on Cytokine Production by Endometrial Cells of Women With Recurrent Spontaneous Abortion

..BUT THERE IS STILL NO SURE ANSWER!

2

CONCLUSION(S): Considering the complex network of immunoregulation at the fetomaternal interface, potential beneficial effects of vitamin D3 in patients with URSA need to be investigated in clinical practice. Comparable levels of 1,25(OH)2D3 production and similar trend of cytokine expression by WECs of URSA and control groups after vitamin D3 treatment reflect the same local metabolic machinery of this hormone.

1

WIDER IMPLICATIONS OF THE FINDINGS

Assessment of vitamin D level is recommended in women with RPL. Vitamin D supplementation should be explored further as a possible therapeutic option for RPL.

[1]Ota, Kuniaki, 2014. "*Vitamin D Deficiency May Be a Risk Factor for Recurrent Pregnancy Losses by Increasing Cellular Immunity and Autoimmunity*." Human Reproduction (Oxford, England) 29 (2): 208–19. doi:10.1093/humrep/det424.

[2]Tavakoli, Maryam. 2011. "Effects of 1,25(OH)2 Vitamin D3 on Cytokine Production by Endometrial Cells of Women with Recurrent Spontaneous Abortion." Fertility and Sterility 96 (3): 751–57. doi:10.1016/j.fertnstert.2011.06.075.

BED REST



"THERAPEUTIC" BED REST CONTINUES TO BE USED WIDELY, DESPITE EVIDENCE OF NO BENEFIT AND KNOWN HARMS:

- ✓ LOSS OF TRABECULAR BONE DENSITY
- ✓ VENOUS THROMBOEMBOLISM RISK
- ✓ MUSCULO-SKELETAL DECONDITIONING
- ✓ SIGNIFICANT PSYCHOSOCIAL STRAIN ON INDIVIDUALS AND FAMILIES

Goldenberg RL, Cliver SP, Bronstein J, et al. Bed rest in pregnancy. Obstet Gynecol 1994; 84:131
(Obstet Gynecol 2013;121:1305–8) DOI: 10.1097/AOG.0b013e318293f12f

PELVIC REST

Pelvic rest might be recommended in conditions such as placenta previa, increased risk of preterm labor or abdominal surgery during pregnancy.

"PELVIC REST" CONSISTS OF AVOIDING ACTIVITIES THAT MIGHT INCREASE PELVIC PRESSURE OR PELVIC MUSCLE CONTRACTIONS, INCLUDING:

- SEX
- DOUCHING
- USE OF TAMPONS
- REPETITIVE SQUATTING
- BRISK WALKING OR OTHER LOWER BODY EXERCISES



Mayo Clinic Guide, www.mayoclinic.org/healthy-lifestyle/pregnancy-week-by-week/in-depth/pregnancy/art-20048007

HEAVY ALCOHOL USE DURING PREGNANCY CAN LEAD TO MISCARRIAGE, STILLBIRTH AND CAN CAUSE THE FETAL ALCOHOL SYNDROME



The effects that alcohol has on a developing baby depend on:

- the seize of the exposure
- the stage of the pregnancy
- The contemporary consumption of other drugs
- traits passed down through the families, still not completely clear



Subst Use Misuse. 2014 Sep; 49(11): 1437–1445.,doi: 10.3109/10826084.2014.912228
Volume and Type of Alcohol during Early Pregnancy and the Risk of Miscarriage
Lyndsay Ammon Avalos, PhD, MPH,a Sarah Roberts, DrPH,b Lee Ann Kaskutas, DrPH,c,d Gladys Block, PhD,d and De-Kun Li, MD, PhDa

Prepregnancy Low to Moderate Alcohol Intake Is Not Associated with Risk of Spontaneous Abortion or Stillbirth[1,2,3]

Audrey J Gaskins[4,*], Janet W Rich–Edwards[5,7,8], Paige L Williams[5,6], Thomas L Toth[10], Stacey A Missmer[5,7,9,11], and Jorge E Chavarro[4,5,7]

But…

- **THESE RESULTS PROVIDE REASSURING EVIDENCE THAT LOW TO MODERATE ALCOHOL INTAKE BEFORE PREGNANCY INITIATION DOES NOT AFFECT RISK OF PREGNANCY LOSS**

Prepregnancy Low to Moderate Alcohol Intake Is Not Associated with Risk of Spontaneous Abortion or Stillbirth., J Nutr. 2016 Mar 9., Gaskins AJ, Rich-Edwards JW, Chavarro JE. DOI: 10.3945/jn.115.226423

CAFFEINE ABUSE PRE- AND IN PREGNANCY MUST BE AVOIDED

Pre-pregnancy caffeine and caffeinated beverage intake and risk of spontaneous abortion.

Gaskins AJ, Rich-Edwards JW, Williams PL, Toth TL, Missmer SA, Chavarro JE.
Eur J Nutr. 2016 Aug 29:1-11

Public Health Nutr. 2016 May;19(7):1233-44. doi: 10.1017/S1368980015002463. Epub 2015 Sep 2.

Maternal caffeine intake during pregnancy and risk of pregnancy loss: a categorical and dose-response meta-analysis of prospective studies.

Chen LW[1], Wu Y[1], Neelakantan N[1], Chong MF[2], Pan A[1], van Dam RM[1].

- Pre-pregnancy coffee consumption at levels ≥4 servings/day is associated with increased risk of sab, particularly at weeks 8-19.
- HIGHER MATERNAL CAFFEINE INTAKE WAS ASSOCIATED WITH A HIGHER RISK OF PREGNANCY LOSS AND ADHERENCE TO GUIDELINES TO AVOID HIGH CAFFEINE INTAKE DURING PREGNANCY APPEARS PRUDENT

World Health Organization

WHO recommendations

For pregnant women with high daily caffeine intake (more than 300 mg per day), lowering daily caffeine intake during pregnancy is recommended to reduce the risk of pregnancy loss and low birth weight neonates.

INFECTIONS: A REAL PROBLEM



- The association of systemic infections with malaria, brucellosis, cytomegalovirus and human immunodeficiency virus, dengue fever, influenza virus and of vaginal infection with bacterial vaginosis, with increased risk of miscarriage has been demonstrated.
- Q fever, adeno-associated virus, bocavirus, hepatitis C and *mycoplasma genitalium* infections do not appear to affect pregnancy outcome.
- The effects of *chlamydia trachomatis, toxoplasma gondii*, human papillomavirus, herpes simplex virus, parvovirus B19, hepatitis B and polyomavirus BK infections remain controversial.

Though various pathogens have been associated with miscarriage, the mechanism(s) of infection-induced miscarriage are not yet fully elucidated.

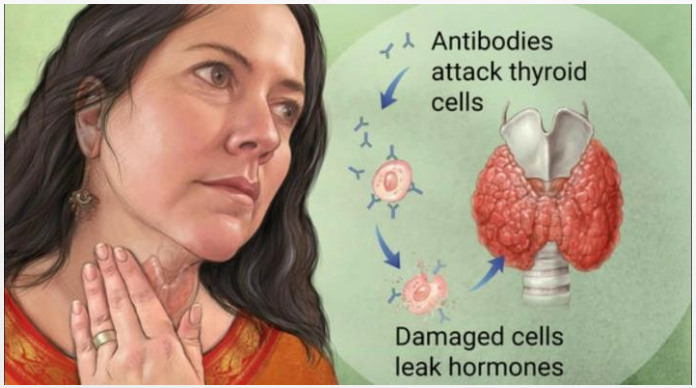
The role of infection in miscarriage, Hum Reprod Update. 2016 Jan; 22(1): 116–133, S. Giakoumelou, Nick Wheelhouse,2 Kate Cuschieri,3 Gary Entrican,2,4 Sarah E.M. Howie,5 and Andrew W. Horne1,* . doi: 10.1093/humupd/dmv041 PMCID: PMC4664130

MISCARRIAGE & PCOS: problems'overlap

- **Miscarriage rates among women with PCOS are believed to be increased** compared with normal fertile women, although supporting evidence is limited. Pregnant women with PCOS experience a higher incidence of perinatal morbidity from **gestational diabetes, pregnancy-induced hypertension, and preeclampsia.**
- The use of insulin sensitizing drugs to decrease hyperinsulinemic insulin resistance has been proposed during pregnancy to reduce the risk of developing preeclampsia or gestational diabetes.
- Administration of **metformin** throughout pregnancy to women with PCOS was associated with a **marked and significant reduction in the rate of early pregnancy loss**[2].

Pregnancy Complications in Women with PCOS, C.M. Boomsma,, University Medical Center Utrecht, Utrecht, The Netherlands, Semin Reprod Med 2008; 26(1): 072-084 DOI: 10.1055/s-2007-992927
2 Metformin reduces abortion in pregnant women with polycystic ovary syndrome, Gynecological Endocrinology Vol. 22 , Iss. 12,2006, , Sherif Khattab, Iman Abdel Mohsen, Ismail Aboul Foutouh,

THYROIDITIS & MISCARRIAGE: still unclear



Thyroid. 2014 Nov;24(11):1642-9. doi: 10.1089/thy.2014.0029. Epub 2014 Sep 17.

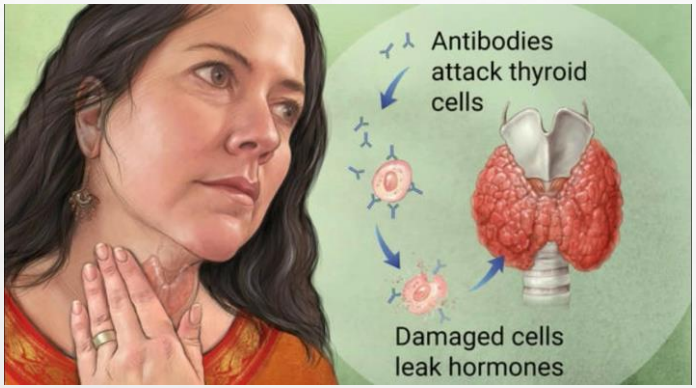
Maternal subclinical hypothyroidism, thyroid autoimmunity, and the risk of miscarriage: a prospective cohort study.

Liu H[1], Shan Z, Li C, Mao J, Xie X, Wang W, Fan C, Wang H, Zhang H, Han C, Wang X, Liu X, Fan Y, Bao S, Teng W.

Conclusion: Women with subclinical hypothyroidism and thyroid autoimmunity are at an increased risk of miscarriage between four and eight gestational weeks.

- Women with a combination of SCH and TAI were found to have the highest risk and earlier gestational ages of miscarriage.
- In this prospective cohort study, 3315 women at low risk for thyroid dysfunction were screened at 4-8 weeks GA
- TSH, fT4, and the autoantibodies TPOAb and TgAb were measured.

THYROIDITIS & MISCARRIAGE: still unclear



Tohoku J Exp Med. 2017 Jul;242(3):167-172. doi: 10.1620/tjem.242.167.

Women with Subclinical Hypothyroidism Are at Low Risk of Poor Pregnancy Outcome in Japan.

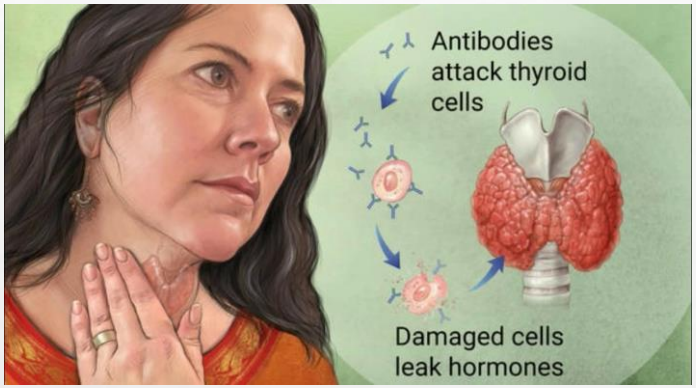
Furukawa S[1], Miyakawa K[2], Shibata J[3], Iwashita M[1].

THE REPLY!

Abstract

Maternal subclinical hypothyroidism may be associated with adverse pregnancy outcomes, although not consistently across regions. Here, we sought to determine the effect of elevated thyroid-stimulating hormone (TSH) on pregnancy outcomes in Japanese women without known medical complications. TSH was determined by dried blood spots at 8-20 weeks of gestation, and 3.0-10.0 μU/mL of TSH was considered as elevated TSH (eTSH). A retrospective study involving 167 cases of eTSH was conducted. Five hundred and seventy eight of controls with normal TSH and without thyroid antibodies were selected. We compared a composite adverse maternal outcome comprised of spontaneous abortion, premature delivery, gestational diabetes mellitus (GDM), placental abruption, and pregnancy-induced hypertension, as well as composite adverse neonatal outcome including stillbirths, heavy for date, light for date, and a low Apgar score (< 7) at 5 minutes between two groups. The incidence of GDM was significantly higher in eTSH ($p < 0.01$); however, composite adverse maternal and neonatal outcome did not differ between groups ($p = 0.19$ and $p = 0.50$, respectively). Although 27 out of 167 cases in eTSH have antibodies, composite adverse outcome did not differ between eTSH with antibodies and controls ($p = 0.64$ and $p = 0.50$, respectively). Additionally, composite adverse maternal and neonatal outcome did not differ between the group larger than the median of TSH in eTSH ($n = 81$) and controls ($p = 0.43$ and $p = 0.98$, respectively). Thus, elevated TSH is not associated with overall adverse pregnancy outcomes in women without known medical complications.

IS IODINE SUPPLEMENTATION NEEDED?



Cochrane Database Syst Rev. 2017 Mar 5;3:CD011761. doi: 10.1002/14651858.CD011761.pub2.

Iodine supplementation for women during the preconception, pregnancy and postpartum period.

Harding KB[1], Peña-Rosas JP[2], Webster AC[3], Yap CM[4], Payne BA[5], Ota E[6], De-Regil LM[1].

- ✓ It may be unethical to compare iodine to placebo or no treatment in severe deficiency settings
- ✓ Trials may also be unfeasible in settings where pregnant and lactating women commonly take prenatal supplements with iodine

Conclusion: UPS AND DOWNS

The available evidence suggested that iodine supplementation decreases the likelihood of postpartum hyperthyroidism and increases the likelihood of the adverse effect of digestive intolerance in pregnancy

PRE-ECLAMPSIA-COMPLICATED PREGNANCIES → Low Dose ASPIRINE?

Ultrasound Obstet Gynecol. 2013 May;41(5):491-9. doi: 10.1002/uog.12421.

Prevention of perinatal death and adverse perinatal outcome using low-dose aspirin: a meta-analysis.

Roberge S[1], Nicolaides KH, Demers S, Villa P, Bujold E.

YES, with correct timing!

CONCLUSION: Low-dose aspirin initiated at ≤ 16 weeks of gestation is associated with a greater reduction of perinatal death and other adverse perinatal outcomes than when initiated at >16 weeks.

Inclusion criteria were risk factors for Pre-Eclampsia, including:

- Nulliparity
- Multiple pregnancy
- Chronic hypertension
- Cardiovascular or endocrine disease
- Prior gestational hypertension or fetal growth restriction
- Abnormal uterine artery doppler

SO, CAN **ANTICOAGULANTS** BE HELPFUL ALSO IN PATIENTS WITH UNEXPLAINED RECURRENT MISCARRIAGE?



Cochrane Database of Systematic Reviews

Aspirin and/or heparin for women with unexplained recurrent miscarriage with or without inherited thrombophilia

New search | Review | Intervention

Paulien G de Jong ✉, Stef Kaandorp, Marcello Di Nisio, Mariëtte Goddijn, Saskia Middeldorp

First published: 4 July 2014

Authors' conclusions

There is a limited number of studies on the efficacy and safety of aspirin and heparin in women with a history of at least two unexplained miscarriages with or without inherited thrombophilia. Of the nine reviewed studies quality varied, different treatments were studied and of the studies at low risk of bias only one was placebo-controlled. No beneficial effect of anticoagulants in studies at low risk of bias was found. Therefore, this review does not support the use of anticoagulants in women with unexplained recurrent miscarriage. The effect of anticoagulants in women with unexplained recurrent miscarriage and inherited thrombophilia needs to be assessed in further randomised controlled trials; at present there is no evidence of a beneficial effect.

Does NOT seem so!

PROGESTERON in RECURRENT MISCARRIAGE

Supplementation with progestogens in the first trimester of pregnancy to prevent miscarriage in women with unexplained recurrent miscarriage: a systematic review and meta-analysis of randomized, controlled trials

Gabriele Saccone, M.D., Corina Schoen, M.D., Jason M. Franasiak, M.D., Richard T. Scott Jr., M.D., H.C.L.D., Vincenzo Berghella, M.D.

Fertility and Sterility® February 2017 Volume 107, Issue 2, Pages 430–438.e3

Conclusion(s)

Our findings provide evidence that supplementation with progestogens may reduce the incidence of recurrent miscarriages and seem to be safe for the fetuses. Synthetic progestogens, including weekly IM 17-hydroxyprogesterone caproate, but not natural P, were associated with a lower risk of recurrent miscarriage. Given the limitations of the studies included in our meta-analysis, it is difficult to recommend route and dose of progestogen therapy. Further head-to-head trials of P types, dosing, and route of administration are required.

Insufficient progesteron production has been believed to be a cause of recurrent miscarriage for some years[1]

This study suggests that SUPPLEMENTATION CAN ACTUALLY PREVENT ADVERSE EVENTS!



[1] Haas, David M, and Patrick S Ramsey. 2013. *"Progestogen for Preventing Miscarriage."* In Cochrane Database of Systematic Reviews. John Wiley & Sons, Ltd. http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003511.pub3/abstract.

IMMUNOTHERAPY can actually prevent MISCARRIAGE?



1

Background

Because immunological aberrations might be the cause of miscarriage in some women, several immunotherapies have been used to treat women with otherwise unexplained recurrent pregnancy loss.

Objectives

The objective of this review was to assess the effects of any immunotherapy, including paternal leukocyte immunization and intravenous immunoglobulin on the live birth rate in women with previous unexplained recurrent miscarriages.

2

Corticosteroid therapy in assisted reproduction – immune suppression is a faulty premise

2

failure after IVF, and recurrent miscarriage (Fox *et al.*, 2016). The immune system is central to establishing receptivity and initiating pregnancy, with resident immune cells modulating the decidual response, epithelial-embryo attachment, trophoblast invasion, vascular adaptation, immune tolerance and cytokine balance (van Mourik *et al.*, 2009; Robertson *et al.*, 2015). Immune

1

Authors' conclusions

Paternal cell immunization, third-party donor leukocytes, trophoblast membranes, and intravenous immunoglobulin provide no significant beneficial effect over placebo in improving the live birth rate.



[1] Wong,, Luchin .2014. “Immunotherapy for Recurrent Miscarriage.” In Cochrane Database of Systematic Reviews. John Wiley & Sons, Ltd. doi/10.1002/14651858.CD000112.pub3/abstract.

[2] Gynecology 41 (5): 491–99. doi:10.1002/uog.12421. Robertson, Sarah A., .2016. “Corticosteroid Therapy in Assisted Reproduction – Immune Suppression Is a Faulty Premise.” Human Reproduction 31 (10): 2164–73. doi:10.1093/humrep/dew186.

Impact of the problem

Major complication of pregnancy associated with perinatal mortality and morbidity.

The incidence of preterm delivery is incresing (9.1-13.4%), even if the neonatal care is improved

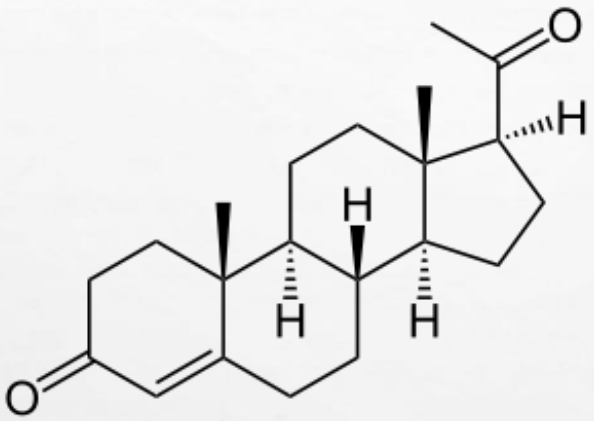
Several risk factors:

- ✓ **Ethnicity**
- ✓ **Previous preterm delivery**
- ✓ **Cervical lenght (< 25 mm before 24 weeks of gestation)**
- ✓ **Conization**
- ✓ **Prolonged vaginal bleeding during pregnancy**
- ✓ **Urinary and vaginal infections, periodontal diseases**
- ✓ **Low Body mass index**
- ✓ **Smoking**
- ✓ **Drugs**
- ✓ **Short interval between pregnancies**

2. Prevenzione del parto pretermine

Blencowe H et al. Lancet 2012; 379: 2162-72
Goldenberg RL et al. Lancet 2008; 371: 75-84
Iams JD, Berghella V. Am J Obstet Gynecol 2010; 89-100

Progesterone



A female sex hormone produced mainly in the ovaries following ovulation each month.

It's a crucial part of the menstrual cycle and maintenance of pregnancy

Symptoms of low progesterone in <u>non</u> pregnant women include:

- ✓ headaches or migraines
- ✓ mood changes, including anxiety or depression
- ✓ low sex drive
- ✓ hot flashes
- ✓ irregularity in your menstrual cycle

Progesterone helps to regulate the cycle and, after ovulation, it helps thicken the lining of the uterus in preparation for a fertilized egg

- Progesterone is a steroid hormone initially produced by the corpus luteum.
- In early pregnancy, progesterone is critical for pregnancy maintenance until the placenta takes over this function at 7 to 9 weeks of gestation, Its name is derived from this function: **pro-gestational steroidal ketone.**
- Removal of the source of progesterone (the corpus luteum) or administration of a progesterone receptor antagonist readily induces abortion before 7 weeks (49 days) of gestation.

MECHANISMS OF ACTION

- Local increase in progesterone in gestational tissue
- Relaxation of myometrial smooth muscle
- Blocking of the action of oxytocin
- Down-regulate gap junctions formation
- Inhibit cervical ripening

in pregnancy

1. Society of Maternal-Fetal Medicine Publications Committee with Berghella V. Progesterone and Preterm Birth Prevention: Translating Clinical Trials Data into Clinical Practice. AJOG. March 2012.
2. Meis PJ, et al. Prevention of Recurrent Preterm Delivery by 17 Alpha-Hydroxyprogesterone Caproate. The New England Journal of Medicine. 12 Jun 2003. 148:24. 2379-85.

17 OH Hydroxyprogesterone caproate

"...approved Makena (hydroxyprogesterone caproate) injection *to reduce the risk of preterm delivery before 37 weeks of pregnancy, in pregnant women with a history of at least one spontaneous preterm birth.*

... not intended for use in women with a multiple pregnancy...

...An international trial is ongoing to learn if there is also improvement in the *outcome of babies* born to women given Makena.

... once a week by injection into the hip.

Treatment should *begin at 16 weeks and no later than 21 weeks of pregnancy.*"

Meis, NEGM 2003
37% vs 55%
Delivery < 37 sg

Northen AT,
Green J 2007
No impact on neonatale outcome

FDA, 2011

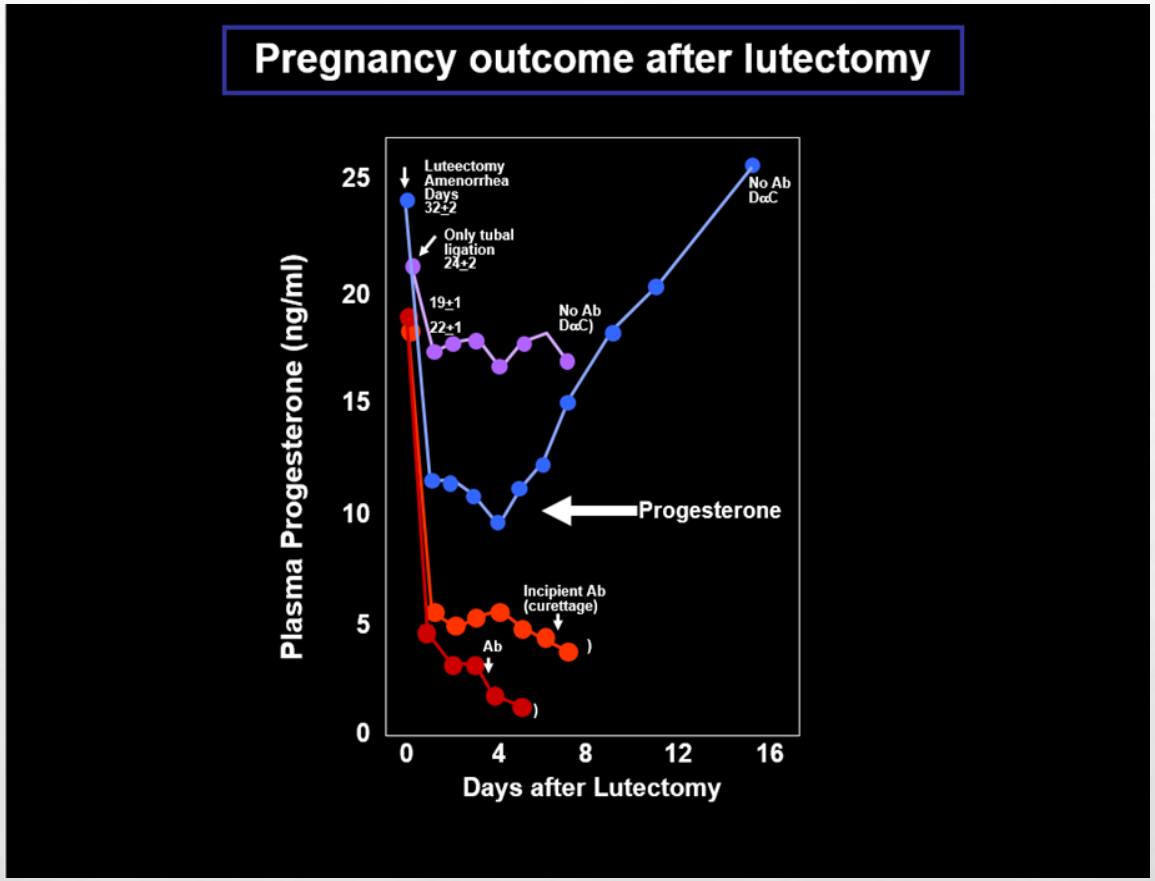
Possible acute effects:

Pain, swelling or itching at the injection site
Rash
Nausea
Diarrhea
Pulmonary edema
infection

Vaginal progesterone

Table 1. Effect of Vaginal Progesterone on the Rate of Preterm Birth in Women With Short Cervix: Results of Randomized Controlled Clinical Trials

Reference	Participants	Criteria	Dosing	Group	Group	*P* Value
Fonseca et al[16]	250	CL ≤15 mm	200-mg capsule once daily, 24 to 34 weeks	19.2%	34.4%	.02
DeFranco et al[26]	46	CL <28 mm	Gel 90 mg once daily, 20[b] to 37[c] weeks	0	29.6%	.014
Hassan et al[20]	458	CL = 10 to 20 mm	Gel 90 mg once daily, 20[d] to 37 weeks	8.9%	16.1%	.02



Luteectomized patients Treated with Progesterone exhibited *Elevated Progesterone* and only a slight and transient decline in estradiol-17P levels and *No evolution of intrauterine pressure and oxytocin response*

Normal pregnancy was sustained.

Csapo A. I. et al, Effects of luteectomy and progesterone replacement therapy in early pregnant patients, American Journal of Obstetrics and Gynecology, 1973: 759-765

CONTROINDICATIONS

- Hypersensitivity to progesterone products
- History of venous or arterial thrombosis
- Carcinoma of breast or genital tract
- Undiagnosed abnormal vaginal bleeding unrelated to pregnancy
- Hepatic disease

1. Progesterone. Lexicomp. Accessed 2 Oct 2016. 2. Hydroxyprogesterone caproate. Lexicomp. Accessed 2 Oct 2016.

SEVERAL STUDIES.....

- DIFFERENT POPULATIONS (SINGLETON VS TWIN PREGNANCIES)
- DIFFERENT INCLUSION CRITERIA
- DIFFERENT TYPES OF TREATMENT (VAGINAL VS INTRAMUSCULUM)
- DIFFERENT AIM OF STUDIES (PROFILAXIS VS TREATMENT)

...HARDLY COMPARABLE

ASYNTOMATIC, SINGLETON PREGNANCY

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Progesterone and the Risk of Preterm Birth among Women with a Short Cervix

Eduardo B. Fonseca, M.D., Ebru Celik, M.D., Mauro Parra, M.D., Mandeep Singh, M.D., and Kypros H. Nicolaides, M.D., for the Fetal Medicine Foundation Second Trimester Screening Group*

N Engl J Med 2007;357:462-9.
Copyright © 2007 Massachusetts Medical Society.

- Cervical length ≤ 15 mm
- Ultrasonography measurement of cervical length at 20 to 25 weeks of gestation
- DAILY VAGINAL ADMINISTRATION
- 200 MG OF PROGESTERONE
- FROM 24 TO 34 WEEKS OF GESTATION

- Significant reduction of spontaneous preterm delivery
- No significant reduction in perinatal mortality or neonatal morbidity.

ASYNTOMATIC, SINGLETON PREGNANCY

Ultrasound Obstet Gynecol 2011; 38: 18–31
Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/uog.9017

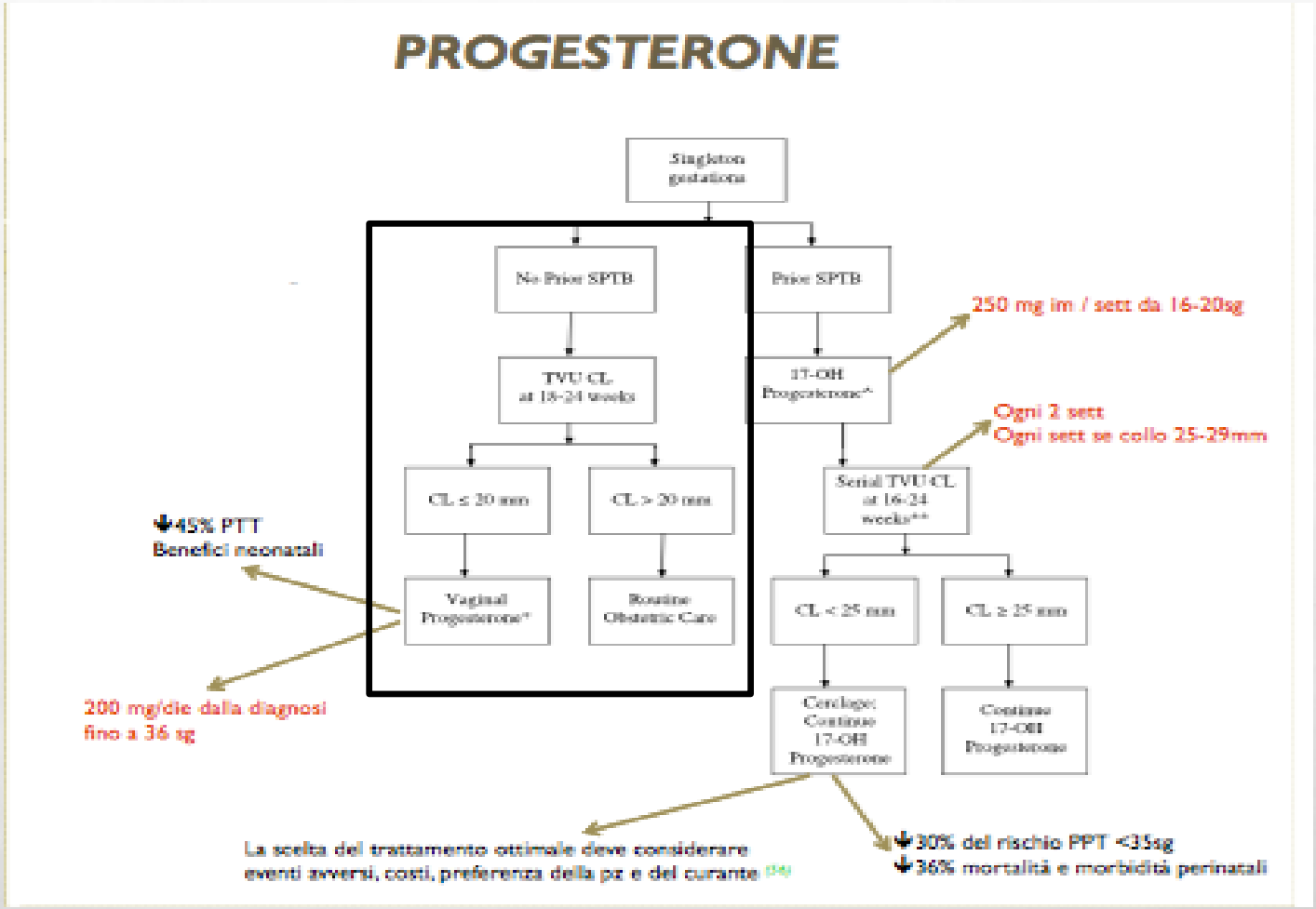
Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: a multicenter, randomized, double-blind, placebo-controlled trial

S. S. HASSAN[1,2], R. ROMERO[1,3,4], D. VIDYADHARI[5], S. FUSEY[6], J. K. BAXTER[7], M. KHANDELWAL[8], J. VIJAYARAGHAVAN[9], Y. TRIVEDI[10], P. SOMA-PILLAY[11], P. SAMBAREY[12], A. DAYAL[13], V. POTAPOV[14], J. O'BRIEN[15,16], V. ASTAKHOV[17], O. YUZKO[18], W. KINZLER[19], B. DATTEL[20], H. SEHDEV[21], L. MAZHEIKA[22], D. MANCHULENKO[23], M. T. GERVASI[24], L. SULLIVAN[25], A. CONDE-AGUDELO[1], J. A. PHILLIPS[26] and G. W. CREASY[27], for the PREGNANT Trial

A sonographic short cervix (10–20 mm) at 19+0 to 23+6 weeks of gestation.
Women were allocated randomly to receive vaginal progesterone gel or placebo daily starting from 20 to 23+6 weeks until 36+6 weeks, rupture of membranes or delivery

45% reduction in the rate of preterm birth before 33 weeks of gestation and
with improved neonatal outcome

Universal Cervical Screening



Berghella V. Universal Cervical Screening for Prediction and Prevention of Preterm Birth
Obstetrical and Gynecological Survey 2012; 67(10): 453-457

ASYNTOMATIC, SINGLETON PREGNANCY

Vaginal progesterone prophylaxis for preterm birth (the OPPTIMUM study): a multicentre, randomised, double-blind trial

Jane Elizabeth Norman, Neil Marlow, Claudia-Martina Messow, Andrew Shennan, Phillip R Bennett, Steven Thornton, Stephen C Robson, Alex McConnachie, Stavros Petrou, Neil J Sebire, Tina Lavender, Sonia Whyte, John Norrie, for the OPPTIMUM study group

Lancet 2016; 387: 2106-16

- **No Significant reduction of spontaneous preterm delivery (≤34 weeks) or composite neonatal adverse outcomes**

- **Cervical length ≤ 25 mm OR previous spontaneous birth at ≤34 weeks of gestation OR positive fetal fibronectin test combined with other clinical risk factors for preterm birth**
- **Enrollment between 18–24 weeks of gestation**
- **DAILY VAGINAL ADMINISTRATION**
- **200 MG OF PROGESTERONE**
- **FROM 22-24 WEEKS OF GESTATION**

ASYNTOMATIC, SINGLETON PREGNANCY

Ultrasound Obstet Gynecol 2016; 48: 308–317
Published online 19 July 2016 in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.15953. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

Vaginal progesterone decreases preterm birth ≤ 34 weeks of gestation in women with a singleton pregnancy and a short cervix: an updated meta-analysis including data from the OPPTIMUM study

R. ROMERO*†‡§, K. H. NICOLAIDES¶, A. CONDE-AGUDELO*, J. M. O'BRIEN**, E. CETINGOZ††, E. DA FONSECA‡‡, G. W. CREASY§§ and S. S. HASSAN*¶¶

Reply...

- **REAFFIRMS THAT VAGINAL PROGESTERONE REDUCES THE RISK OF PRETERM BIRTH AND NEONATAL MORBIDITY AND MORTALITY FOR WOMEN WITH SINGLETON GESTATION AND SHORT CERVIX.**

BIAS

- META-ANALYSIS, JULY 2016
- 5 TRIALS, INCLUDING OPPTIMUM
- Information on the Bayley-III cognitive composite score at 2years of age, one of the primary outcome measures, was available for only ~70% of children
- No results for key outcomes such as preterm birth<37, <32, and<28weeks of gestation, RDS, Retinopathy of prematurity and birth weight<1500g and<2500g, among others
- Only 68.6% of women (66.3% in the vaginal progesterone group) used at least 80% of study
- Most primary and secondary outcome measures were incompletely reported for the three subgroups of women at risk of preterm birth so they cannot be included in the meta-analyses

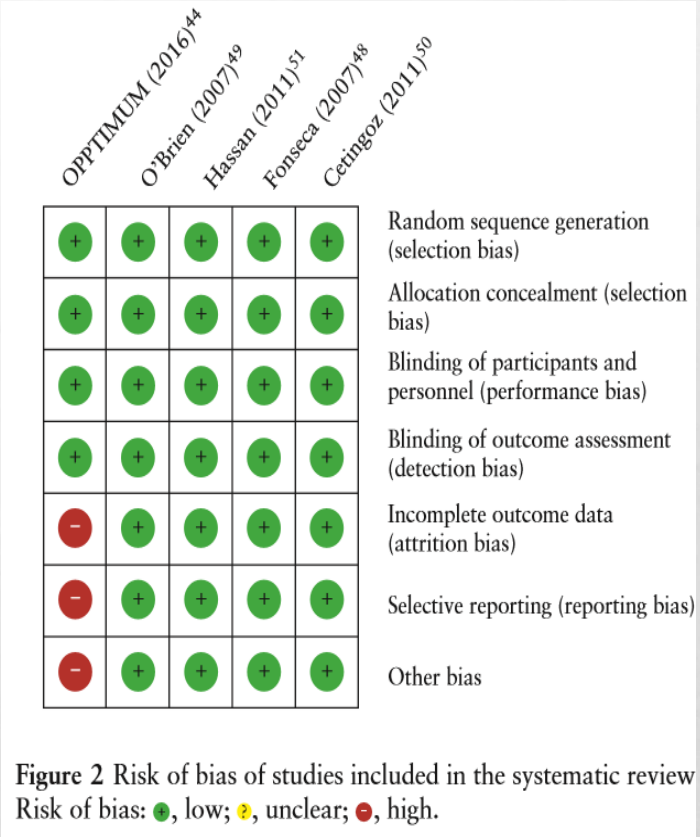


Figure 2 Risk of bias of studies included in the systematic review
Risk of bias: +, low; ?, unclear; -, high.

1. Romero R et al. Vaginal progesterone decreases preterm birth≤34weeks of gestation in women with a singleton pregnancy and a short cervix: an updated meta-analysis including data from the OPPTIMUM study Ultrasound Obstet Gynecol 2016; 48: 308–317

ASYNTOMATIC, SINGLETON PREGNANCY WITH PREVIOUS PRETERM BIRTH

Ultrasound Obstet Gynecol 2007; 30: 687–696
Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/uog.5158

Progesterone vaginal gel for the reduction of recurrent preterm birth: primary results from a randomized, double-blind, placebo-controlled trial

J. M. O'BRIEN[1], C. D. ADAIR[2], D. F. LEWIS[3], D. R. HALL[4], E. A. DEFRANCO[5], S. FUSEY[6], P. SOMA-PILLAY[7], K. PORTER[8], H. HOW[9], R. SCHACKIS[10], D. ELLER[11], Y. TRIVEDI[12], G. VANBUREN[13], M. KHANDELWAL[14], K. TROFATTER[15], D. VIDYADHARI[16], J. VIJAYARAGHAVAN[17], J. WEEKS[18], B. DATTEL[19], E. NEWTON[20], C. CHAZOTTE[21], G. VALENZUELA[22], P. CALDA[23], M. BSHARAT[24] and G. W. CREASY[25]

- Spontaneous singleton preterm birth at between 20+0 and 35+0 weeks of gestation in the immediately preceding pregnancy
- Women enrolled between 18+0 and 22+6 weeks of gestation
- DAILY VAGINAL ADMINISTRATION
- 1.125 G OF GEL CONTAINING 90 MG OF PROGESTERONE
- FROM ENROLLMENT TO 37 WEEKS OF GESTATION

- No Significant reduction of spontaneous preterm delivery (≤32 weeks) in women with a history of spontaneous preterm birth

ASYNTOMATIC, SINGLETON PREGNANCY WITH PREVIOUS PRETERM BIRTH WITH CERCLAGE

Am J Obstet Gynecol. 2010 April ; 202(4): 351.e1–351.e6. doi:10.1016/j.ajog.2010.02.019.

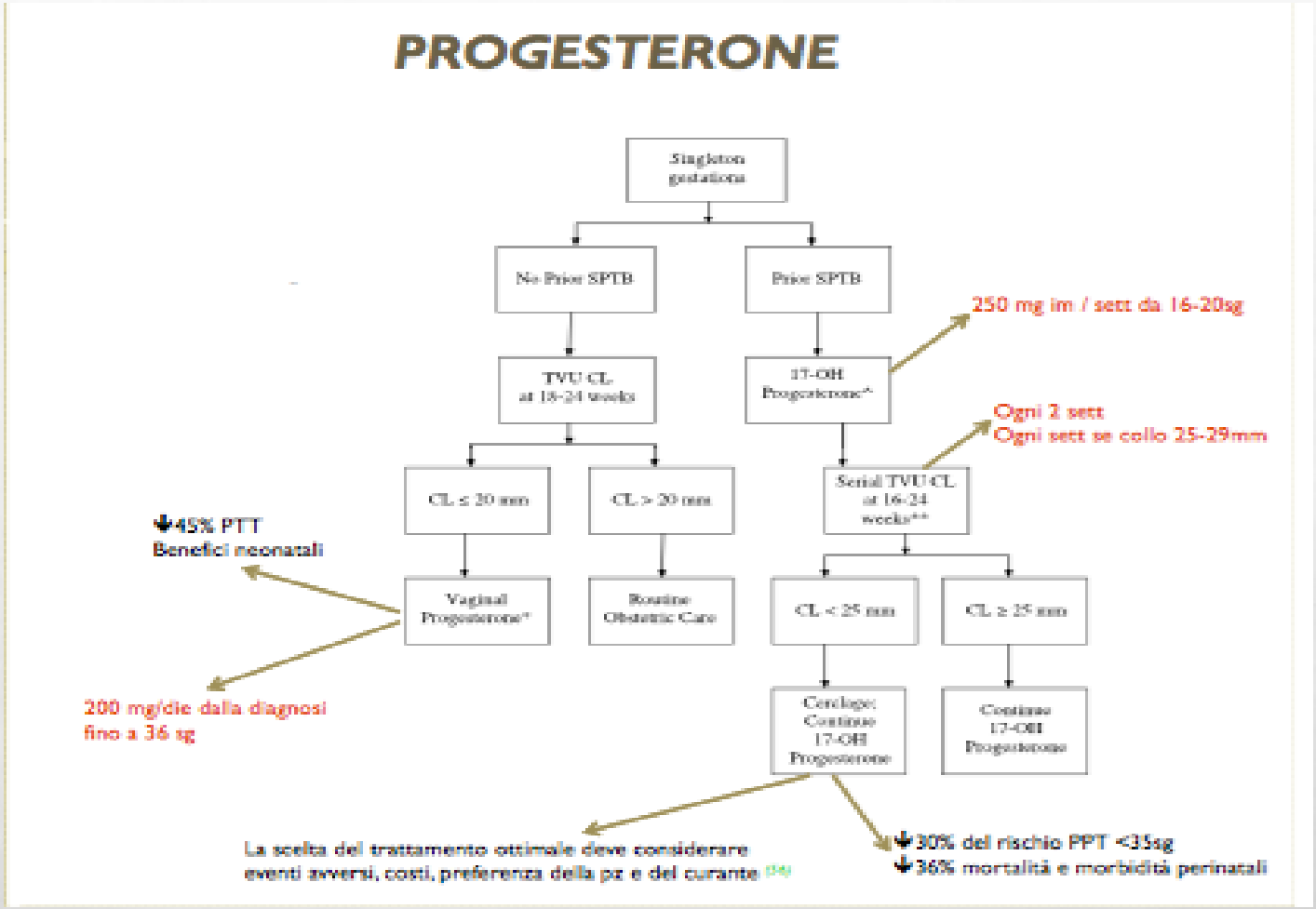
17 alpha-hydroxyprogesterone caproate for the prevention of preterm birth in women with prior preterm birth and a short cervical length

Vincenzo BERGHELLA, MD[1], Dana FIGUEROA, MD[2], Jeff M. SZYCHOWSKI, PhD[3], John OWEN, MD[2], Gary HANKINS, MD[4], Jay D. IAMS, MD[5], Jeanne S. SHEFFIELD, MD[6], Annette Perez-DELBOY, MD[7], Deborah A. WING, MD[8], and Edwin R. GUZMAN, MD[9] for the Vaginal Ultrasound Trial Consortium

- **No additional benefit for prevention of preterm delivery (≤35 weeks) in women with cerclage**
- **In the absence of cerclage, 17P was associated with a reduction in previable birth and perinatal mortality**

- **Spontaneous singleton preterm birth at between 17+0 and 33+0 weeks of gestation in previous pregnancy**
- **Cervical length ≤ 15 mm measured between 16 and 22 weeks of gestation**
- **WEEKLY INTRAMUSCOLAR ADMINISTRATION**
- **250 MG OF 17-ALPHAHYDROXYPROGESTERONE CAPROATE (17P)**
- **FROM 16 TO 36 WEEKS OF GESTATION**

Universal Cervical Screening



Berghella V. Universal Cervical Screening for Prediction and Prevention of Preterm Birth
Obstetrical and Gynecological Survey 2012; 67(10): 453-457

ASYNTOMATIC, SINGLETON PREGNANCY WITH PREVIOUS PRETERM BIRTH

Ultrasound Obstet Gynecol 2017
Published online in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.17245

Vaginal progesterone *vs* intramuscular 17α-hydroxy-progesterone caproate for prevention of recurrent spontaneous preterm birth in singleton gestations: systematic review and meta-analysis of randomized controlled trials

G. SACCONE*, A. KHALIFEH†, A. ELIMIAN‡, E. BAHRAMI§, K. CHAMAN-ARA¶, M. A. BAHRAMI** and V. BERGHELLA†

- **Spontaneous singleton preterm birth in previous pregnancy**
- **Women enrolled at about 16 weeks' gestation daily vaginal administration**
- **90 MG OF PROGESTERONE (GEL),**
- **100 OR 200 MG VAGINAL CPR DAILY**
- **250 MG INTRAMUSCULAR WEEKLY**
- **FROM ENROLLMENT TO 36 WEEKS OF GESTATION OR DELIVERY**

- **Significant reduction of spontaneous preterm delivery (≤34 weeks) in women with a history of spontaneous preterm birth**
- **Daily vaginal progesterone started at about 16 weeks' gestation is a reasonable, if not better, alternative to weekly 17-OHPC injection**

ASYNTOMATIC, TWIN PREGNANCY

Vaginal progesterone decreases preterm birth and neonatal morbidity and mortality in women with a twin gestation and a short cervix: An updated meta-analysis of individual patient data

Roberto Romero[1,2,3,4,*], Agustin Conde-Agudelo[1,5], Waleed El-Refaie[6], Line Rode[7,8], Maria L. Brizot[9], Elcin Cetingoz[10], Vicente Serra[11,12], Eduardo Da Fonseca[13], Mohamed S. Abdelhafez[6], Ann Tabor[7,14], Alfredo Perales[12,15], Sonia S. Hassan[1,5] and Kypros H. Nicolaides[16]

DOI: 10.1002/uog.17397

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Issue



Ultrasound in Obstetrics & Gynecology

Accepted Article

Accepted manuscript online: 9 January 2017

- Cervical length ≤ 25 mm
- DAILY VAGINAL ADMINISTRATION
- 200 MG OF PROGESTERONE IN 3TRIALS:
  -1 00 MG OF PROGESTERONE IN 1 TRIAL
  -400 MG OF PROGESTERONE IN 1 TRIAL
  -200/400 MG OF PROGESTERONE IN 1 TRIAL
- FROM 20-24 WEEKS OF GESTATION IN 5 TRIALS,
- FROM 18-21 WEEKS OF GESTATION IN 1 TRIAL

- Significant reduction of spontaneous preterm delivery (≤33 weeks) by 31%
- Larger-than-average reduction in the risk of preterm birth <33 weeks
- CL between 10-20 mm, vaginal progesterone 400 mg/day

HIGH RISK PREGNANCIES

Arch Gynecol Obstet (2011) 283:423–429
DOI 10.1007/s00404-009-1351-2

MATERNO-FETAL MEDICINE

Progesterone effects on preterm birth in high-risk pregnancies: a randomized placebo-controlled trial

Elcin Cetingoz · Cetin Cam · Mustafa Sakallı · Ates Karateke · Cem Celik · Ali Sancak

Received: 9 April 2009 / Accepted: 29 December 2009 / Published online: 22 January 2010
© Springer-Verlag 2010

Risk groups **included prior spontaneous preterm birth, twin pregnancy, and uterine malformations.**

Micronized progesterone or placebo (100 mg) **was administered daily by vaginal suppository between 24 and 34 weeks of gestation.**

Prophylactic **vaginal progesterone reduced the rate of preterm labor and preterm delivery in high-risk pregnancies**

Administering progesterone also reduced the preterm birth before 34 weeks of gestation

Cochrane Library

Cochrane Database of Systematic Reviews

Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth (Review)

Dodd JM, Jones L, Flenady V, Cincotta R, Crowther CA

Cochrane Database of Systematic Reviews 2013, Issue 7. Art. No.: CD004947.

Selection criteria

Randomised controlled trials, in which progesterone was given for preventing preterm birth.

Data collection and analysis

Two review authors independently evaluated trials for methodological quality and extracted data.

Progesterone versus placebo for women with a past history of spontaneous preterm birth

Progesterone was associated with a statistically significant reduction in the risk of perinatal mortality (six studies; 1453 women; risk ratio (RR) 0.50, 95% confidence interval (CI) 0.33 to 0.75), preterm birth less than 34 weeks (five studies; 602 women; average RR 0.31, 95% CI 0.14 to 0.69), infant birthweight less than 2500 g (four studies; 692 infants; RR 0.58, 95% CI 0.42 to 0.79), use of assisted ventilation (three studies; 633 women; RR 0.40, 95% CI 0.18 to 0.90), necrotising enterocolitis (three studies; 1170 women; RR 0.30, 95% CI 0.10 to 0.89), neonatal death (six studies; 1453 women; RR 0.45, 95% CI 0.27 to 0.76), admission to neonatal intensive care unit (three studies; 389 women; RR 0.24, 95% CI 0.14 to 0.40), preterm birth less than 37 weeks (10 studies; 1750 women; average RR 0.55, 95% CI 0.42 to 0.74) and a statistically significant increase in pregnancy prolongation in weeks (one study; 148 women; mean difference (MD) 4.47, 95% CI 2.15 to 6.79). No differential effects in terms of route of administration, time of commencing therapy and dose of progesterone were observed for the majority of outcomes examined.

Progesterone versus placebo for women with a short cervix identified on ultrasound

Progesterone was associated with a statistically significant reduction in the risk of preterm birth less than 34 weeks (two studies; 438 women; RR 0.64, 95% CI 0.45 to 0.90), preterm birth at less than 28 weeks' gestation (two studies; 1115 women; RR 0.59, 95% CI 0.37 to 0.93) and increased risk of urticaria in women when compared with placebo (one study; 654 women; RR 5.03, 95% CI 1.11 to 22.78). It was not possible to assess the effect of route of progesterone administration, gestational age at commencing therapy, or total cumulative dose of medication.

Progesterone versus placebo for women with a multiple pregnancy

Progesterone was associated with no statistically significant differences for the reported outcomes.

Progesterone versus placebo for women with 'other' risk factors for preterm birth

Progesterone, was associated with a statistically significant reduction in the risk of infant birthweight less than 2500 g (three studies; 482 infants; RR 0.48, 95% CI 0.25 to 0.91).

The review of 36 randomised controlled trials, involving a total of 8523 women considered to be at increased risk of preterm birth, and 12,515 infants, found that where progesterone was given (by injection into the muscle in some studies and as a pessary into the vagina in others), it had beneficial effects, including reducing the risk of the baby dying after birth, suffering complications such as requiring assisted ventilation, necrotising enterocolitis or requiring admission to neonatal intensive care, prolonging the pregnancy, and reducing the chance of neonatal intensive care admission.

Information related to longer-term infant and childhood outcomes was limited. Overall, the trials included in this review were considered to be of good to fair quality. Further trials are required to assess the optimal timing, mode of administration and dose of administration of progesterone therapy.

MAINTENANCE TREATMENT AFTER AN ARRESTED PRETERM LABOUR, SINGLETON PREGNANCY

BJOG An International Journal of Obstetrics and Gynaecology

First published: 30 March 2016

Explore this journal >

General obstetrics

Vaginal progesterone as maintenance treatment after an episode of preterm labour (PROMISE) study: a multicentre, double-blind, randomised, placebo-controlled trial

M Palacio ✉, T Cobo, E Antolín, M Ramirez, F Cabrera, F Mozo de Rosales, JL Bartha, M Juan, A Martí, D Oros, À Rodríguez, E Scazzocchio, JM Olivares, S Varea, J Ríos, E Gratacós,

- **Women admitted for preterm labour, and had been successfully treated with any tocolytic drug**
- **Cervical length ≤ 25 mm**
- **Gestational age between 24.0 and <34.0 weeks of gestation**
- **DAILY VAGINAL ADMINISTRATION**
- **200 MG OF PROGESTERONE**
- **FROM 24 TO 36 WEEKS OF GESTATION**

- **No Significant reduction of spontaneous preterm delivery**

Cochrane Library
Cochrane Database of Systematic Reviews

Progestational agents for treating threatened or established preterm labour (Review)

Su LL, Samuel M, Chong YS

Cochrane Database of Systematic Reviews 2014, Issue 1. Art. No.: CD006770.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (31 August 2013), CENTRAL (*The Cochrane Library* 2013, Issue 10), MEDLINE (1966 to August 31 2013) and Embase (1974 to 31 August 2013). We checked the reference lists of all included studies to identify any additional studies and communicated with authors and the pharmaceutical industry.

Selection criteria

Randomised controlled trials that compared progestational agents, given either alone or in combination with other tocolytics, with a control group receiving another tocolytic, placebo or no treatment, for the treatment of preterm labour.

Data collection and analysis

Two review authors independently extracted data and assessed trial quality.

the use of progestational agents both for prevention as well as treatment of preterm labour have been published. This review of the literature found eight randomised controlled trials involving 563 women, but data from only seven studies from a total of 538 women with threatened or established preterm labour with intact membranes contributed data to this updated review. Four trials compared the use of progestational agents versus placebo in women concurrently treated with another drug to reduce uterine contractions (tocolytic agent). Progesterone was used independently in the other four trials compared with another tocolytic agent or placebo. Limited evidence suggests that the use of a progesterone, as a co-treatment, may reduce preterm deliveries at less than 37 weeks' gestation and increase birthweight. There is insufficient evidence from the seven small studies with contributing data to advocate progestational agents as a tocolytic agent for women presenting with preterm labour.

Authors' conclusions

There is insufficient evidence to advocate progestational agents as a tocolytic for women presenting with preterm labour.

Royal College of Obstetricians and Gynaecologists

Bringing to life the best in women's health care

Use of a tocolytic drug is associated with a prolongation of pregnancy for up to 7 days but with no significant effect on preterm birth and no clear effect on perinatal or neonatal morbidity.

There is no clear evidence that tocolytic drugs improve outcome and therefore it is reasonable not to use them. However, tocolysis should be considered if the few days gained would be put to good use, such as completing a course of corticosteroids or in utero transfer.	A
Use of a tocolytic drug is not associated with a clear reduction in perinatal or neonatal mortality, or neonatal morbidity.	A
Tocolysis may be considered for women with suspected preterm labour who have had an otherwise uncomplicated pregnancy. It is reasonable not to use any tocolytic drug. B	B
Women most likely to benefit from use of a tocolytic drug are those who are in very preterm labour, those needing transfer to a hospital which can provide neonatal intensive care and those who have not yet completed a full course of corticosteroids.	✓
Tocolysis should not be used where there is a contraindication to prolonging pregnancy.	✓
Nifedipine and atosiban have comparable effectiveness in delaying birth for up to seven days.	A
Compared with beta-agonists, nifedipine is associated with improvement in neonatal outcome, although there are no long-term data.	A
Beta-agonists have a high frequency of adverse effects. Nifedipine, atosiban and the COX inhibitors have fewer types of adverse effects, and they occur less frequently than for beta-agonists but how they compare with each other is unclear.	A
Using multiple tocolytic drugs appears to be associated with a higher risk of adverse effects and so should be avoided.	B
There is insufficient evidence for any firm conclusions about whether or not tocolysis leads to any benefit in preterm labour in multiple pregnancy.	✓
There is insufficient evidence for any firm conclusions about whether or not maintenance tocolytic therapy following threatened preterm labour is worthwhile. Thus, maintenance therapy is not recommended.	A

Tocolysis for Women in preterm labour, February 2011

Is bed rest beneficial?

There is no evidence supporting bed rest as an effective intervention for prevention of spontaneous preterm birth in singletons or twins.

Bed rest has known potential promotes:

- ✓ Loss of trabecular bone density
- ✓ Venous thromboembolism risk
- ✓ Musculoskeletal deconditioning
- ✓ Significant psychosocial strain on individuals and families

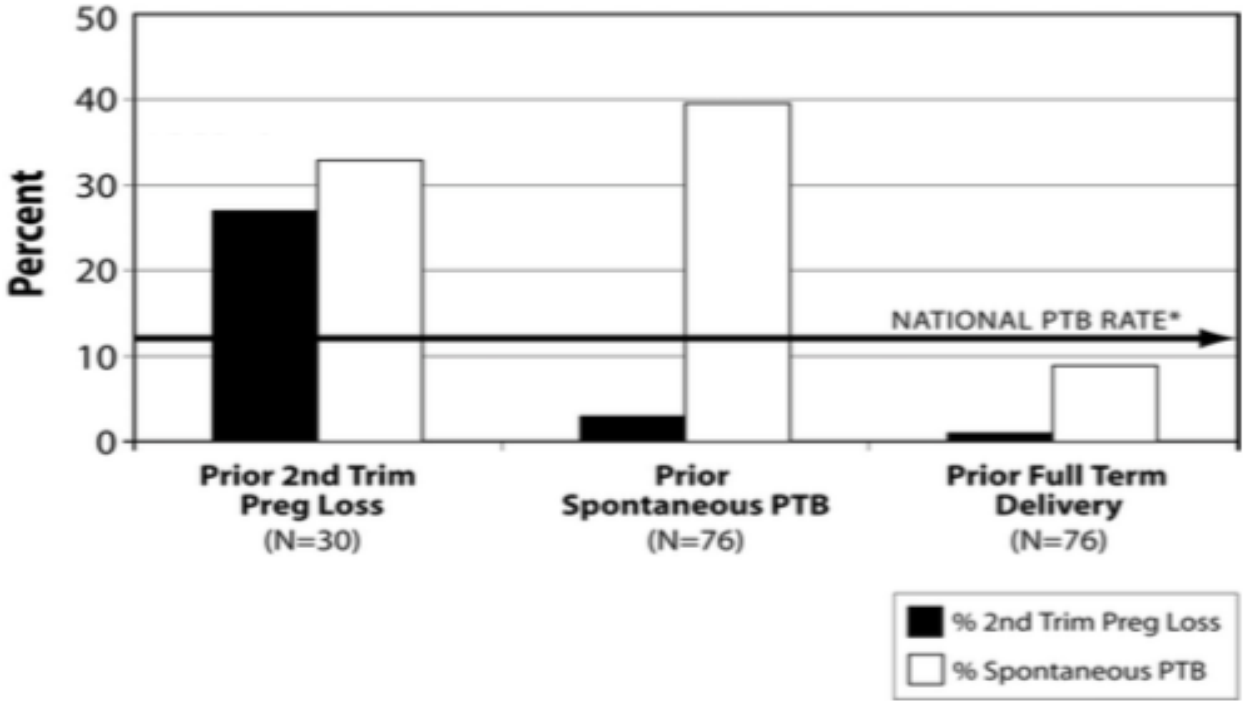
Based on lack of evidence of efficacy in prematurity prevention, and known significant risks, we do not recommend bed rest for women with a recent history of PTL.

The only randomized trial designed to determine whether hospitalization of women with arrested PTL increased the proportion of deliveries ≥36 weeks compared with women discharged home did not find a benefit. In both groups, about 70 percent of women delivered at ≥36 weeks of gestation.

Goldenberg RL. Arrested preterm labor: do the data support home or hospital care? Obstet Gynecol 2005; 106:3.
Goldenberg RL, Cliver SP, Bronstein J, et al. Bed rest in pregnancy. Obstet Gynecol 1994; 84:131
Yost NP, Bloom SL, McIntire DD, Leveno KJ. Hospitalization for women with arrested preterm labor: a randomized trial. Obstet Gynecol 2005; 106:14.

Risk of recurrency

FIGURE 1
Pregnancy outcome after second trimester loss



Subsequent pregnancy outcome in women with prior second trimester loss, prior spontaneous preterm birth, and prior birth at term.

Reproduced, with permission, from Edlow et al.[32]

Iams. Care for women with prior preterm birth. Am J Obstet Gynecol 2010.

LINEE GUIDA

GESTIONE DEL PARTO PRETERMINE

FONDAZIONE CONFALONIERI RAGONESE

SU MANDATO SIGO, AOGOI, AGUI

7.1 Qual è l'efficacia dell'uso del Progesterone nel prevenire il parto pretermine nelle donne considerate a rischio di parto pretermine per:

- **anamnesi positiva di parto pretermine spontanea**
- **anamnesi positiva per rottura pretermine delle membrane**
- **anamnesi positive per aborto del secondo trimestre**
- **anamnesi positiva di trauma cervicale (compresa chirurgia)**
- **cervice corta identificata allecografia e/o per protrusione delle membrane nella gravidanza attuale**

Meis, 2003
Fonseca, 2007

Fonseca, 2007
Hassan, 2011
Romero, 2012

Lo screening universale ecografico della cervicometria nelle donne nullipare condotta per via transvaginale nel II trimestre seguito dalla somministrazione di Progesterone si è dimostrato efficace e "cost-effective" nella riduzione del rischio di parto pretermine in alcuni studi[12,13].

Werner EF, Obstet Gynecol 2011

Raccomandazioni

Si raccomanda la somministrazione profilattica di Progesterone nelle seguenti condizioni:

- Donna con storia precedente di parto pretermine definita come:
  - parto improvviso avvenuto tra 16.6 e 36.6 s.g.
  - parto di feto morto avvenuto nel II trimestre (prima della 24^ sg)
  - rottura delle membrane pretermine (preparto)
  - dilatazione cervicale avanzata o "bulging" delle membrane

- Si raccomanda somministrazione di idrossiprogesterone caproato (17OHPC) 250 mg im/settimanale o Progesterone micronizzato per via vaginale (90-100 mg/die) dalla 16^ alla 36.6^ settimana. (I A)

- Donna asintomatica con riscontro di cervicometria ridotta (10-20 mm) a 19-23.6 settimane:
  - Si raccomanda somministrazione di Progesterone vaginale micronizzato (90 mg/die al mattino) dalla 19^ alla 36.6^ settimana. (I A). La somministrazione di 90 mg/die di Progesterone vaginale micronizzato è risultata equivalente alla somministrazione di 200 mg/die sia in termini di riduzione di rischio di parto pretermine che di riduzione della morbilità e mortalità neonatale.

- L'uso come terapia di mantenimento della tocolisi dopo episodio acuto in pazienti con travaglio pretermine non è correntemente suggerito (I C).
- La somministrazione profilattica di Progesterone (17OHPC o Progesterone vaginale) in donne sottoposte a trachelectomia, conizzazione o trattamento cervicale mediante ansa diatermica non è raccomandata. Tale trattamento è consigliato in caso di modificazioni della lunghezza cervicale (BPC).

ALGORITMO DELLO STUDIO

Paziente con minaccia di parto prematuro

(almeno 4 criteri di inclusione soddisfatti)

OSPEDALIZZAZIONE

Induzione della maturità polmonare (Betametasone 12 mg im x2/die) + tocolitico (Tractocile) (2gg)

Persistenza attività contrattile?

Modificazioni visita ostetrica?

Riduzione cervicometria?

Aumento indici di flogosi?

SI

Esclusione dallo studio:
prosecuzione terapia tocolitica
espletamento del parto

NO

periodicamente

Tamponi cervico-vaginali

Urocoltura

Indici di flogosi sistemici

Lattoferrina

300 mg cpr vaginali

Studio controllato randomizzato in aperto

Progesterone

200 mg ov vag

Registrazione dei dati relativi all'andamento della gravidanza, al parto ed all'outcome neonatale.

A role for pessary?

Literature doesn't agree:
Different inclusion criteria

Twin and singleton pregnancies
Different type of additional treatment (antibiotic, progesterone..)

SINGLETON

EFFECTIVE
Goya et Al 2012

NOT EFFECTIVE
Nicolaides et Al 2016
Hui et Al 2013

MULTIPLE

EFFECTIVE
Goya et Al 2016

NOT EFFECTIVE
Liem et Al 2013
Jarde et Al 2016

- Goya, et al. 2012. "Cervical Pessary in Pregnant Women with a Short Cervix (PECEP): An Open-label Randomised Controlled Trial." *The Lancet* 379 (9828):.
- Nicolaides et al. 2016. "A Randomized Trial of a Cervical Pessary to Prevent Preterm Singleton Birth." *New England Journal of Medicine* 374 (11): 1044–52
- Hui,et al. 2013. "Cerclage Pessary for Preventing Preterm Birth in Women with a Singleton Pregnancy and a Short Cervix at 20 to 24 Weeks: A Randomized Controlled Trial." *American Journal of Perinatology* 30 (04): 283–88.
- Goya et al. et al. 2016. "Cervical Pessary to Prevent Preterm Birth in Women with Twin Gestation and Sonographic Short Cervix: a Multicenter Randomized Controlled Trial (PECEP-Twins)." *American Journal of Obstetrics & Gynecology* 214 (2): 145–52
- Liem et al. 2013 "Cervical Pessaries for Prevention of Preterm Birth in Women with a Multiple Pregnancy (ProTWIN): a Multicentre, Open-label Randomised Controlled Trial." *The Lancet* 382 (9901): 1341–49.
- Jarde et al. 2016 "Effectiveness of Progesterone, Cerclage and Pessary for Preventing Preterm Birth in Singleton Pregnancies: a Systematic Review and Network Meta-analysis." *BJOG: An International Journal of Obstetrics & Gynaecology* 124 (8): 1176–89.

Singleton

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of a Cervical Pessary to Prevent Preter

Kypros H. Nicolaides, M.D., Argyro
Gemma Picciarelli, M.D., Natasa T
Evdoxia Skyfta, M.D., M
Ricardo Palma-Dias, M.D., Ph.D

METHODS

We conducted a multicenter, randomi
placement with expectant managemen
pregnant with singletons (singleton pre
25 mm or less at 20 weeks 0 days to 24
either group who had a cervical length
subsequent visits, received treatment wi
come was spontaneous delivery before

RESULTS

In an intention-to-treat analysis, there
pessary group (465 participants) and t
rate of spontaneous delivery before 34 v
ratio in the pessary group, 1.12; 95% c
There were no significant differences i
pessary group and 2.4% in the control
(6.7% and 5.7%, respectively; P=0.55), c
respectively; P=0.59). The incidence of
significantly higher in the pessary grou

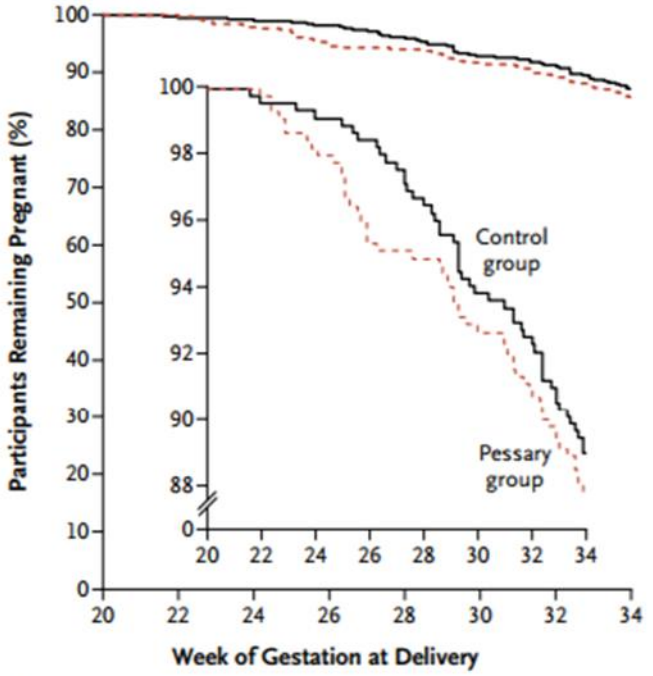


Figure 2. Kaplan–Meier Plot of Continued Pregnancy without Delivery.

Eight participants with iatrogenic delivery before 34 weeks of gestation were excluded from the analysis. The inset shows the same data on an expanded y axis.

Singletons

Cerclage Pessary for Preventing Preterm Birth in Women with a Singleton Pregnancy and a Short Cervix at 20 to 24 Weeks: A Randomized Controlled Trial

Shuk Yi Annie Hui, M.R.C.O.G.[1] Chung Ming Chor, M.R.C.O.G.[1] Tze Kin Lau, M.D., F.R.C.O.G.[2]
Terence T. Lao, M.D., F.R.C.O.G.[1] Tak Yeung Leung, M.D., F.R.C.O.G.[1]

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Am J Perinatol 2013;30:283–288.

Results Among 4438 screened women, 203 women (4.6%) met the inclusion criteria and 108 (58%) consented for the study. A total of 53 and 55 women were allocated to pessary and control groups, respectively. There was no difference in background demographics, including the mean cervical length (19.6 mm versus 20.5 mm) and the mean gestational age at randomization (both 21.9 weeks). Delivery before 34 weeks occurred in 9.4% and 5.5% ($p = 0.46$) in the pessary and the control groups, respectively. No differences in major side effects were noted between the groups.

Conclusion In our population, <5% had a cervical length of less than 25 mm at 20 to 24 weeks' gestation. The prophylactic use of cerclage pessary did not reduce the rate of preterm delivery before 34 weeks.

THE LANCET

Cervical pessaries for prevention of preterm birth in women with a multiple pregnancy (ProTWIN): a multicentre, open-label randomised controlled trial

Dr Sophie Liem, MD, Ewoud Schuit, PhD, Maud Hegeman, MD, Joke Bais, PhD, Karin de Boer, PhD, Kitty Bloemenkamp, PhD, Jozien Brons, PhD, Hans Duvekot, PhD, Bas Nij Bijvank, MD, Maureen Franssen, PhD, Ingrid Gaugler, PhD, Irene de Graaf, PhD, Martijn Oudijk, PhD, Dimitri Papatsonis, PhD, Paula Pernet, MD, Martina Porath, PhD, Liesbeth Scheepers, PhD, Marko Sikkema, PhD, Jan Sporken, PhD, Harry Visser, PhD, Wim van Wijngaarden, PhD, Mallory Woiski, MD, Mariëlle van Pampus, PhD, Prof Ben Willem Mol, PhD, Dick Bekedam, PhD

Methods

We undertook a multicentre, open-label randomised controlled trial in 40 hospitals in the Netherlands. We randomly assigned women with a multiple pregnancy between 12 and 20 weeks' gestation (1:1) to pessary or control groups, using a web-based application with a computer-generated list with random block sizes of two to four, stratified by hospital. Participants and investigators were aware of group allocation. For women in the pessary group, a midwife or obstetrician inserted a cervical pessary between 16 and 20 weeks' gestation. Women in the control group did not receive the pessary, but otherwise received similar obstetrical care to those in the pessary group. The primary outcome was a composite of poor perinatal outcome: stillbirth, periventricular leucomalacia, severe respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular haemorrhage, necrotising enterocolitis, proven sepsis, and neonatal death. Analyses were by modified intention to treat. This trial is registered in the Dutch trial registry, number NTR1858.

Findings

Between Sept 21, 2009, and March 9, 2012, 813 women underwent randomisation, of whom 808 were analysed (401 in the pessary group; 407 in the control group). At least one child of 53 women (13%) in the pessary group had poor perinatal outcome, compared with 55 (14%) in the control group (relative risk 0·98, 95% CI 0·69–1·39).

Interpretation

In unselected women with a multiple pregnancy, prophylactic use of a cervical pessary does not reduce poor perinatal outcome.

Report of Major Impact

TABLE 2
Outcomes according to treatment group

Pregnancy outcome	Pessary (n = 68), no. (range/%)	No treatment (n = 66), no. (range/%)	*P* value	RR (CI 95%)
Spontaneous delivery at <28 wk	4 (5.9)	9 (13.6)	ns	0.43 (0.14—1.33)
Spontaneous delivery at <34 wk	11 (16.2)	26 (39.4)	.003	0.41 (0.22—0.76)
Any delivery at <34 wk	12 (17.6)	27 (40.9)	.002	0.43 (0.24—0.78)
SPB for monochorionic twins	23.0	50.0	.01	
Spontaneous delivery at <37 wk	47 (69.1)	48 (72.7)	ns	0.95 (0.76—1.18)
Gestational age at delivery, wk	35.3 (2.9)	33.1 (3.9)	.01	
Days admitted for threatened preterm delivery	3.5 (2—5)	3.9 (2—6)		
Tocolytic therapy	22 (32.3)	29 (43.9)	ns	0.74 (0.47—1.14)
Corticosteroid treatment for fetal maturation	25 (36.7)	31 (46.9)	ns	0.78 (0.52—1.17)
Chorioamnionitis	2 (3.0)	2 (2.9)	ns	0.97 (0.14—6.70)
PPROM	1 (1.5)	6 (9.1)	ns	0.16 (0.20—1.31)
Cesarean delivery	29 (42.6)	28 (42.4)	ns	1.01 (0.68—1.49)
Vaginal delivery				
Spontaneous	20 (29.5)	21 (31.8)	ns	0.92 (0.55—1.54)
Instrumented	19 (27.9)	17 (25.8)	ns	1.08 (0.62—1.90)
Maternal side effects				
Vaginal discharge	68 (100)	35 (53.0)	.01	—
Pessary repositioning without removal	11 (16.2)	—		—
Pessary replacement	2 (2.9)	—		—
Pregnancy bleeding	3 (4.4)	3 (4.5)	ns	0.97 (0.20—4.64)
Cervical tear	0	0		—
Uterine rupture	0	0		—

Perinatal outcome	Pessary (n = 136), no. (%)	No treatment (n = 130), no. (%)	*P* value	RR (CI 95%)
Fetal death	0	2	ns	—
Neonatal death	0	0	ns	—
Birthweight <1500 g	13 (9.5)	17 (13.1)	ns	0.73 (0.37—1.44)
Birthweight <2500 g	47 (34.6)	62 (47.7)	.01	0.72 (0.54—0.97)
Adverse outcomes				
Necrotizing enterocolitis	0	2 (1.5)	ns	—
Intraventricular hemorrhage[a]	0	4 (3.0)	ns	—
Respiratory distress syndrome	8 (5.9)	8 (6.1)	ns	0.96 (0.37—2.47)
Retinopathy	0	0	ns	—
Treatment for sepsis	4 (2.9)	6 (4.6)	ns	—
Composite adverse outcomes	8 (5.9)	12 (9.1)	ns	0.64 (0.27—1.50)

CI, confidence interval; *ns*, not significant; *PPROM*, preterm prelabour rupture of membranes; *RR*, relative risk; *SPB*, spontaneous preterm birth.

[a] Grade 2 in all infants.

Goya et al. RCT of cervical pessary in twin gestations with short cervix. Am J Obstet Gynecol 2016.

BJOG An International Journal of Obstetrics and Gynaecology

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A randomized controlled trial of cervical cerclage in women at high risk of spontaneous preterm delivery

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Summary. The effect of cervical suture on pregnancy outcome was studied in 194 women with a high risk (approximately 30%) of having a late abortion or a preterm delivery. The women were randomly allocated either to have a cervical suture inserted (n=96) or to be managed without a suture (n=98). There was no evidence that cervical cerclage either prolonged gestation or improved survival. Patients allocated to receive cerclage spent significantly longer in hospital, even when the period of admission for insertion was excluded. The patients in the cerclage group were more likely to receive tocolytic drugs, and more of them experienced puerperal pyrexia, although these differences between the groups were not statistically significant.

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Cervical cerclage for preterm birth prevention in twin gestation with short cervix: a retrospective cohort study

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Methods This was a retrospective cohort study of 40 consecutive DCDA twin gestations at Saint Peter's University Hospital from November 2006 to November 2014 in which cervical cerclage was performed for an ultrasound-determined cervical length of 1–24 mm at 16–24 weeks' gestation. The cases were matched with 40 controls without cerclage for cervical length and gestational age at cervical assessment. The primary outcome measure was spontaneous birth < 32 weeks.

Results There was no difference between the two groups in maternal age, body mass index (BMI), cigarette smoking, use of in-vitro fertilization (IVF), parity and prior spontaneous preterm birth. There were more Caucasian women among the controls compared with cases. In the cases, compared with controls, spontaneous delivery < 32 weeks was significantly less frequent (20.0% vs 50.0%; relative risk, 0.40 (95% CI, 0.20–0.80)). In the prediction of spontaneous delivery < 32 weeks, logistic regression analysis demonstrated that the risk was reduced with the insertion of cervical cerclage (odds ratio, 0.22 (95% CI, 0.058–0.835); P = 0.026), corrected for maternal age, BMI, racial origin, cigarette smoking, IVF, parity and previous preterm birth.

Conclusion In DCDA twin gestation with a short cervix, treatment with cervical cerclage may reduce the rate of early preterm birth. The findings suggest the need for adequate randomized controlled trials on cerclage in twin gestations with a short cervix. Copyright © 2016 ISUOG. Published by John Wiley & Sons Ltd.

Houlihan 2016. "Cervical Cerclage for Preterm Birth Prevention in Twin Gestation with Short Cervix: a Retrospective Cohort Study." *Ultrasound in Obstetrics & Gynecology: The Official Journal of the International Society of Ultrasound in Obstetrics and Gynecology* 48 (6): 752–56.

BJOG An International Journal of Obstetrics and Gynaecology

British Journal of Obstetrics and Gynaecology
June 1993, Vol. 100, pp. 516–523

OBSTETRICS

Final report of the Medical Research Council/Royal College of Obstetricians and Gynaecologists Multicentre Randomised Trial of Cervical Cerclage

MRC/RCOG Working Party on Cervical Cerclage

Results The overall preterm delivery rate was 28%. There were fewer deliveries before 33 weeks in the cerclage group (83 (13%) compared with 110 (17%), P=0·03) and this difference reflected deliveries characterised by features of cervical incompetence (painless cervical dilatation and prelabour rupture of the membranes). There was a corresponding difference in very low birthweight deliveries (63 (10%) compared with 86 (13%), P=0·05). The difference in the overall rate of miscarriage, stillbirth or neonatal death (55 (9%) compared with 68 (11%)) was less marked and was not statistically significant. The use of cervical cerclage was associated with increased medical intervention and a doubling of the risk of puerperal pyrexia.

Conclusions These results suggest that the operation had an important beneficial effect in 1 in 25 cases in the trial (95% confidence interval (CI) 1 in 12 to 1 in 300 sutures). Its use is associated with increased medical intervention and puerperal pyrexia. Nevertheless, this trial suggests that, on balance, cervical cerclage should be offered to women at high risk, such as those with a history of three or more pregnancies ending before 37 weeks gestation.

Macnaughton et al. 1993)

A comparison between devices

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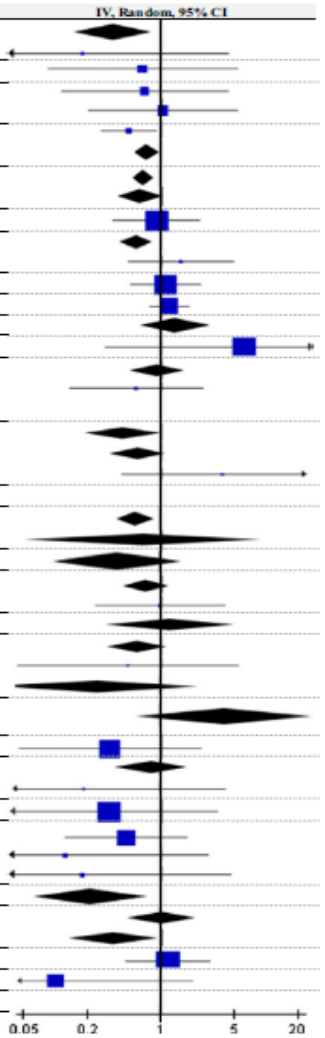
Effectiveness of proges
pessary for preventing p
pregnancies: a systemati
meta-analysis

A Jarde,[a] O Lutsiv,[a] CK Park,[b] J Beyene,[b] JM Dod
AB Biringer,[i] L Sabatino,[j] L Giglia,[k] Z Han,[l] K Stau

Main findings

In this first comprehensive network met
new method for ranking and comparing
preventing PTB in women at risk, prog
to be the best option. Progesterone ranke
clage for most of our outcomes and w
significantly lower odds of PTB < 34
weeks, and NND, among others. Similar
in the subgroup of women with previou
women with a short cervix, where scant
lower odds of only PTB < 34 weeks.
were inconsistencies in rankings and v
evidence overall.

Outcome	Intervention	Studies	N	Tau^2 (I^2)	OR/MD (95% CI)
Preterm birth <24 weeks	Cerclage	2	258	0.00 (0%)	**0.37 (0.17, 0.82)**
	Pessary	1	108	-	0.20 (0.01, 4.27)
Preterm birth <26 weeks	Pessary	1	108	-	0.33 (0.03, 3.31)
Preterm birth <30 weeks	Cerclage	1	101	-	0.72 (0.11, 4.50)
	Pessary	1	108	-	1.04 (0.20, 5.40)
Preterm birth <33 weeks	Progesterone	1	458	-	**0.51 (0.29, 0.90)**
	Cerclage	3	1,733	0.00 (0%)	**0.75 (0.57, 0.98)**
Preterm birth <35 weeks	Progesterone	4	2,185	0.00 (0%)	**0.70 (0.57, 0.86)**
	Cerclage	3	474	0.00 (0%)	0.68 (0.45, 1.04)
Preterm birth <36 weeks	Cerclage	1	506	-	0.88 (0.36, 2.16)
Birth weight <1,500g	Progesterone	4	1,637	0.00 (0%)	**0.59 (0.42-0.84)**
	Pessary	1	509	-	1.54 (0.50-4.76)
Small for gestational age (<3%)	Progesterone	1	651	-	1.09 (0.52, 2.30)
Small for gestational age (<10%)	Progesterone	1	651	-	1.20 (0.78, 1.84)
Congenital anomalies	Progesterone	5	2,259	0.00 (0%)	1.36 (0.63, 2.93)
Miscarriage	Progesterone	1*	459	-	5.60 (0.31,101.94)
Stillbirth	Progesterone	7*	3,537	0.07 (10%)	0.91 (0.51, 1.63)
	Cerclage	1	253	-	0.59 (0.14, 2.50)
	Pessary	0*	0	-	Not estimable
Perinatal death	Progesterone	3	641	0.08 (12%)	0.44 (0.19, 1.00)
	Cerclage	5	1,123	0.05 (9%)	0.60 (0.33, 1.09)
	Pessary	1	509	-	3.84 (0.43, 34.63)
Umbilical cord pH †	Progesterone	1	100	-	-0.00 (-0.02, 0.01)
Respiratory distress syndrome	Progesterone	7	2,482	0.12 (43%)	**0.59 (0.39, 0.88)**
	Pessary	2	488	3.00 (86%)	0.67 (0.05, 8.90)
Mechanical ventilation	Progesterone	2	487	0.50 (28%)	0.40 (0.10, 1.59)
Bronchopulmonary dysplasia	Progesterone	6	2,883	0.00 (0%)	0.71 (0.43, 1.17)
	Cerclage	1	244	-	0.98 (0.24, 4.02)
Intraventricular hemorrhage (III-IV)	Progesterone	4*	2,169	0.00 (0%)	1.23 (0.30, 5.01)
Intraventricular hemorrhage (I-IV)	Progesterone	5	2,042	0.07 (11%)	0.60 (0.31, 1.15)
	Cerclage	1	244	-	0.49 (0.04, 5.45)
	Pessary	2	488	0.00 (0%)	0.26 (0.03, 2.33)
Periventricular leukomalacia	Progesterone	2*	783	0.00 (0%)	3.76 (0.61, 23.05)
Necrotizing enterocolitis (II-III)	Progesterone	1*	642	-	0.40 (0.08, 2.07)
Necrotizing enterocolitis	Progesterone	5	2,781	0.23 (29%)	0.83 (0.38, 1.83)
	Pessary	1	380	-	0.20 (0.01, 4.15)
Retinopathy of prematurity (III-IV)	Progesterone	1	642	-	0.33 (0.03, 3.22)
Retinopathy of prematurity (I-IV)	Progesterone	1	457	-	0.49 (0.14, 1.72)
	Cerclage	1	244	-	0.14 (0.01, 2.68)
	Pessary	1	380	-	0.20 (0.01, 4.15)
Sepsis (onset <72h)	Progesterone	2	783	0.00 (0%)	**0.23 (0.07, 0.75)**
Sepsis (overall)	Progesterone	4*	1,107	0.00 (0%)	1.05 (0.50, 2.21)
	Pessary	2	488	0.00 (0%)	**0.35 (0.13, 0.93)**
Neonatal jaundice	Pessary	1	108	-	1.16 (0.49, 2.71)
Maternal mortality	Cerclage	1	35	-	0.10 (0.00, 2.07)
Antepartum hospital stay †	Cerclage	1*	194	-	**5.47 (3.63, 7.31)**



Diamonds indicate pooled effect size of meta-analyses; individual studies are represented by blocks and lines. N = sample size; OR = Odds Ratio; MD=Mean Difference
* The effect size was not estimable for one study. The non-estimable study is not included in the number of studies and its sample size is not included in the n-value. See Figure S4.1 to S4.54 for individual study data.
† Diamond point not shown because outcome is not binary (*i.e.* result is not OR)

Figure 1. Results of pairwise meta-analyses for secondary outcomes with too few studies to do a network meta-analysis. [Colour figure can be viewed at wileyonlinelibrary.com]

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Systematic review

Preterm birth prevention in twin pregnancies with progesterone, pessary, or cerclage: a systematic review and meta-analysis

A Jarde,[a] O Lutsiv,[a] CK Park,[b] J Barrett,[c] J Beyene,[b] S Saito,[d] JM Dodd,[e] PS Shah,[f] JL Cook,[g] AB Biringer,[h] L Giglia,[i] Z Han,[j] K Staub,[k] W Mundle,[l] C Vera,[m] L Sabatino,[n] SK Liyanage,[a] SD McDonald[a]

Background About half of twin pregnancies deliver preterm, and it is unclear whether any intervention reduces this risk.

Objectives To assess the evidence for the effectiveness of progesterone, cerclage, and pessary in twin pregnancies.

Search strategy We searched Medline, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials, and ISI Web of Science, without language restrictions, up to 25 January 2016.

Selection criteria Randomised controlled trials of progesterone, cerclage, or pessary for preventing preterm birth in women with twin pregnancies, without symptoms of threatened preterm labour.

Data collection and analysis Two independent reviewers extracted data using a piloted form. Study quality was appraised with the Cochrane Risk of Bias tool. We performed pairwise inverse variance random-effects meta-analyses.

Main results We included 23 trials (all but three were considered to have a low risk of bias) comprising 6626 women with twin pregnancies. None of the interventions significantly reduced the risk of preterm birth overall at <34 or <37 weeks of gestation, or neonatal death, our primary outcomes, compared to a control group. In women receiving vaginal progesterone, the relative risk (RR) of preterm birth <34 weeks of gestation was 0.82 (95% CI 0.64–1.05, seven studies, I^2 36%), with a significant reduction in some key secondary outcomes, including very low birthweight (<1500 g, RR 0.71, 95% CI 0.52–0.98, four studies, I^2 46%) and mechanical ventilation (RR 0.61, 95% CI 0.45–0.82, four studies, I^2 22%).

Conclusion In twin gestations, although no overarching intervention was beneficial for the prevention of preterm birth and its sequelae, vaginal progesterone improved some important secondary outcomes.

Keywords Cerclage, pessary, preterm birth, progesterone, randomised controlled trials, twin.

Tweetable abstract Vaginal progesterone may be beneficial in twin pregnancies, but not 17-OHPC, cerclage, or pessary.

Linked article This article is commented on by V Berghella and G Saccone, p. 1174 in this issue. To view this mini commentary visit https://doi.org/10.1111/1471-0528.14533. This article is also commented on by JR Biggio Jr, p. 1175 in this issue. To view this mini commentary visit https://doi.org/10.1111/1471-0528.14551.

Jarde 2017 2017. "Effectiveness of Progesterone, Cerclage and Pessary for Preventing Preterm Birth in Singleton Pregnancies: a Systematic Review and Network Meta-analysis." *BJOG: An International Journal of Obstetrics & Gynaecology* 124 (8): 1176–89.







