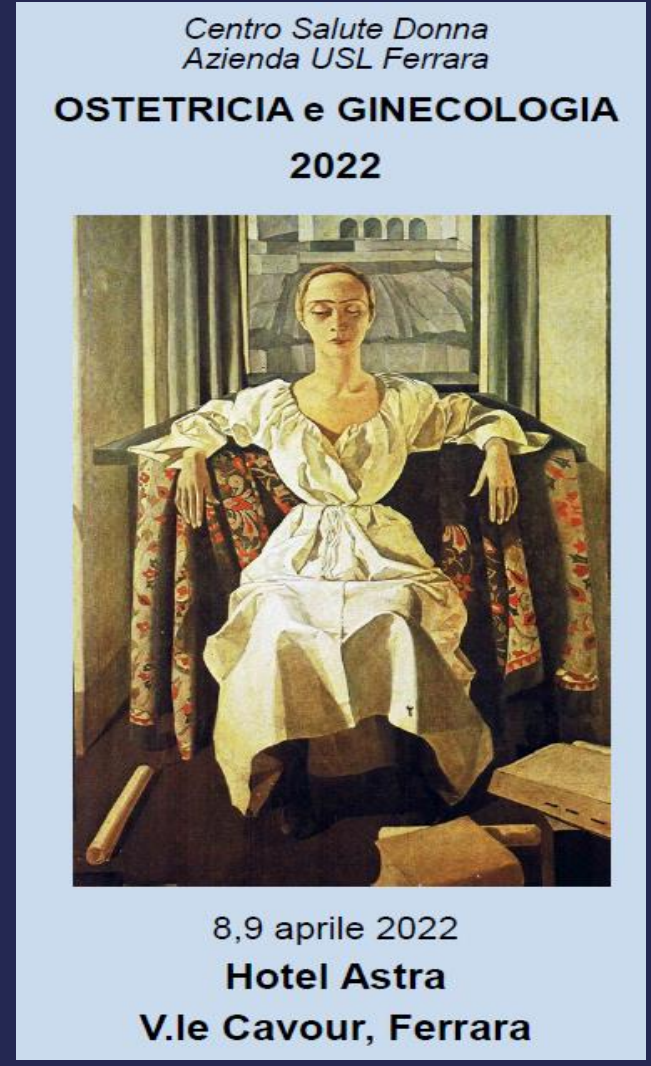
MINACCIA D'ABORTO: ACCURATEZZA DIAGNOSTICA, PROTOCOLLI TERAPEUTICI NEBULOSI E REALTÀ CONSULTORIALE

Dott.ssa Claudia Guaraldi

FERRARA 9 APRILE 2022

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Unità Sanitaria Locale di Ferrara



DEFINIZIONE

- La minaccia d'aborto si caratterizza per una perdita ematica vaginale durante la gravidanza che non incontra i criteri diagnostici dell'aborto spontaneo
- prima della 20a settimana di gestazione
- WHO: “pregnancy -related bloody vaginal discharge or franck bleeding during the first half of pregnancy without cervical dilatation”

- Circa il 25% delle gravidanze presentano un qualche grado di sanguinamento nel primo trimestre; di queste circa il 50% esitano in aborto spontaneo

SEGNI E SINTOMI

- perdita ematiche genitale da lieve a moderata
- nessun passaggio di tessuti o prodotto del concepimento dal canale cervicale
- Cervice chiusa
- embrione vitale
- può associarsi anche dolore addominale, dolore lombare , senso di peso sovrapubico

- LA DIAGNOSI VIENE EFFETTUATA SIA CON L'ESAME PELVICO CHE CON L'ECOGRAFIA TV PER VALUTARE SIA LA VITALITA' DELL'EMBRIONE SIA CHE LA CERVICE CHIUSA

RUOLO DELL'ECOGRAFIA: Linee Guida SIEOG

Raccomandazione 5

Nelle donne sintomatiche con dolore o perdita ematica vaginale in gravida <13 settimane, ed in quelle con ecografia non diagnostica o gravidanza a localizzazione incerta, si raccomanda la esecuzione di ecografia transvaginale, considerata strumento diagnostico di scelta per la diagnosi di gravidanza extrauterina tubarica con sensibilità dell'87-99% e specificità del 94-99,9%.

- RACCOMANDAZIONE POSITIVA FORTE
- RACCOMANDAZIONE TRATTA DA LINEE GUIDA DI QUALITÀ ALTA

Raccomandazione 6

In caso di dolore o perdita ematica vaginale in gravida <13 settimane, o di ecografia non diagnostica o gravidanza a localizzazione incerta, è raccomandato informare la donna dei limiti della accuratezza della diagnosi di aborto spontaneo con una singola ecografia, in particolare ad epoche gestazionali precoci.

- RACCOMANDAZIONE POSITIVA FORTE
- RACCOMANDAZIONE TRATTA DA LINEE GUIDA DI QUALITÀ ALTA

DIAGNOSI DI ABORTO SPONTANEO

Analisi della letteratura ed interpretazione delle prove

Le Line Guida NICE 2019b raccomandano nel caso di non visualizzazione del battito cardiaco embrionale di misurare la lunghezza vertice-sacro e di misurare il diametro medio del sacco gestazionale solo se il polo embrio/fetale non è visibile.

Se la lunghezza vertice-sacro è inferiore a 7,0 mm con un'ecografia transvaginale e non è visibile alcun battito cardiaco o il diametro medio del sacco gestazionale è inferiore a 25,0 mm con un'ecografia transvaginale e non è presente alcun polo embrio/fetale visibile, è raccomandato eseguire una seconda ecografia ad un intervallo minimo di 7 giorni dalla prima.

Si può formulare diagnosi di aborto interno se:

- non si visualizza l'attività cardiaca in un embrione con lunghezza vertice-sacro uguale o superiore a 7,0 mm all'ecografia transvaginale, oppure
- non si visualizza l'attività cardiaca in un embrione con lunghezza vertice-sacro uguale o superiore a 10,0 mm all'ecografia transaddominale, oppure
- non si visualizza l'embrione in un sacco gestazionale con diametro medio uguale o superiore a 25,0 mm.

Il pannello di esperti ha considerato il fatto che in Italia gli esami ecografici (con la sola esclusione di alcune ecografie di supporto alla visita clinica) sono eseguiti da medici-chirurghi e non anche da operatori non medici come in Gran Bretagna. Pertanto, non si è ritenuta applicabile al contesto assistenziale italiano la necessità di far confermare la diagnosi di aborto interno in questi casi da un secondo operatore come invece suggerito dal NICE.

Secondo le indicazioni date dal NICE (2019b) si può formulare diagnosi di aborto completo se non si evidenzia tessuto trofoblastico all'interno della cavità uterina in paziente nella quale una precedente ecografia ha dimostrato la presenza di camera gestazionale intrauterina. In assenza di una precedente ecografia ben documentata, la gravidanza va descritta come gravidanza a localizzazione sconosciuta. Va consigliato a queste donne di eseguire il follow-up (hCG, ecografie) fino a quando non si ottiene una diagnosi definitiva.

Si può formulare diagnosi di aborto incompleto se si evidenzia la presenza all'interno della cavità uterina di echi iperecogeni, ben definiti, da riferire a tessuto trofoblastico, con frequente evidenza di vascolarizzazione (a differenza dei coaguli, mal definiti e avascolari), in paziente nella quale una pregressa ecografia ha dimostrato la presenza di camera gestazionale intrauterina.

EZIOLOGIA

- L'eziologia della minaccia d'aborto e dell'aborto spontaneo è spesso sconosciuta
- **Gli aborti spontanei** nel 50 % dei casi sono dovuti ad anomalie cromosomiche, quindi saranno comunque non prevenibili e non modificabili

Altri fattori di rischio di **aborto spontaneo** (a volte modificabili a volte non modificabili):

- anomalie strutturali dell'utero
- esposizione a sostanze tossiche (lavorative) o teratogene
- Esposizione a sostenze stupefacenti, alcool, fumo
- infezioni virali o batteriche nelle prime settimane di gravidanza
- salute materna: diabete scompensato, malattie tiroidee scompensate, stato nutrizionale non ottimale sia in eccesso che in difetto
- Fattori immunologici: alterazione del processo di regolazione del riconoscimento immunologico tra gli antigeni materni e quelli fetali
- trombofilie
- età materna e paterna avanzate
- Eventi trumatici, violenza domestica

PREVENZIONE DELL'ABORTO SPONTANEO

- Con il counselling preconcezionale possiamo a volte intervenire sui fattori di rischio modificabili, quali il compenso di malattie metaboliche, la correzione di malformazioni uterine, l'intervento sugli stili di vita e/o l'allontanamento da un ambiente di lavoro malsano.
- Ricordiamo che l'aborto spontaneo anche quando ricorrente, spesso, non è correlabile ad una patologia ben definita, e la sua causa rimane inspiegata (abortività ricorrente idiopatica)

- Epidemiologia:
- I dati indicano inoltre che una minaccia d'aborto possa presentarsi in ogni gravidanza, indipendentemente da età materna, razza, stato socioeconomico e stile di vita; una gravida che abbia avuto un sanguinamento nel primo trimestre in una passata gravidanza ha un rischio aumentato che ciò succeda anche in una successiva
- Più aborti spontanei ha avuto una donna, maggiore è il rischio che l'abbia in una gravidanza successiva

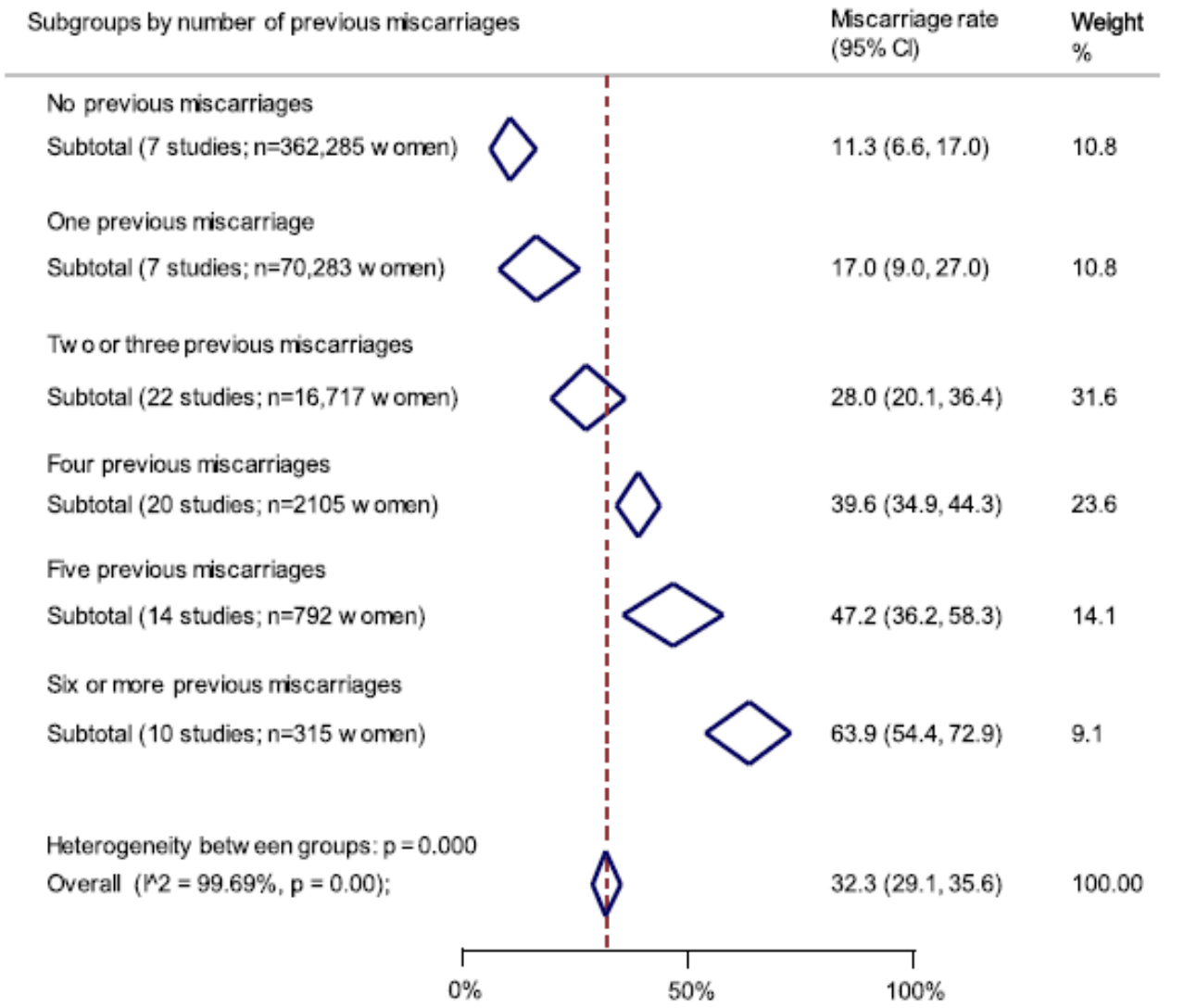


Fig. 1. Risk of miscarriage by the number of previous miscarriages: a meta-analysis. *Systematic review methods: Databases: MEDLINE, EMBASE, CCTR, CDSR, DARE; Search period: From respective database inception to June 2019; Search terms (MESH): Recurrent miscarriage (habitual abortion, pregnancy loss, fetal loss, foetal loss, fetal demise) AND prediction and prognosis (significance, score, marker, role, index, indicator, nomogram, forecast, goal, calculate, estimate, project, likelihood, extrapolate, implication or prototype); Review Outcome: Miscarriage categorised by previous number previous pregnancy losses.*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Sporadic pregnancy loss and recurrent miscarriage

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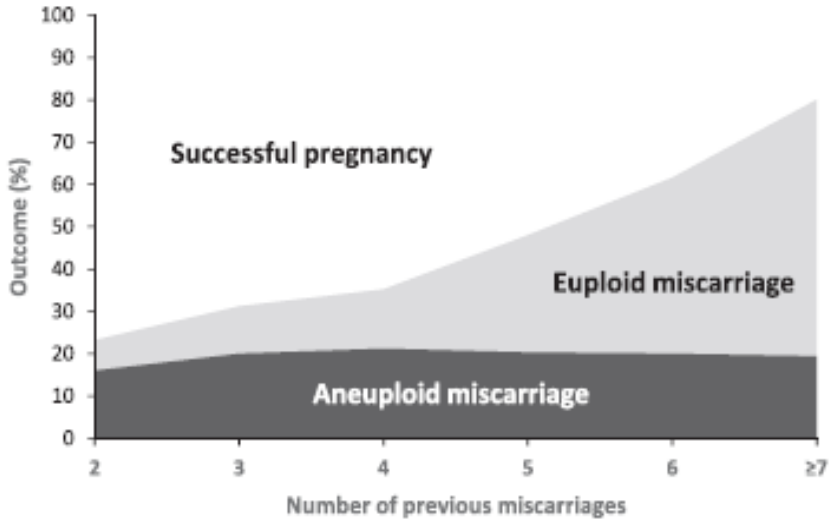

Fig. 2. Risk of aneuploid and euploid miscarriages by the number of previous miscarriages.

VALUTAZIONE CLINICA DELLA MINACCIA D'ABORTO

- La storia clinica, un esame pelvico ed un'ecografia transvaginale/transaddominale sono mandatori per stabilire se ci troviamo di fronte ad una minaccia d'aborto o ad un quadro di aborto spontaneo/in atto
- Nelle prime settimane di gravidanza può essere utile anche un dosaggio del beta HCG
- La diagnosi differenziale va fatta oltre che con l'aborto spontaneo propriamente detto con le IVU, cerviciti e/o patologie neoplastiche causa di sanguinamento vaginale, polipi del c.c. o altre cause di sanguinamento del collo uterino

EMATOMA SUBCORIALE

- Approximately 18% of women with first-trimester vaginal bleeding and an IUP will be diagnosed with a subchorionic hemorrhage. If the hematoma seen is less than 25% of the gestational sac area, then the prognosis for the pregnancy generally is good. However, subchorionic hematomas are associated with an increased risk of miscarriage, as well as late pregnancy loss and complications.
- La presenza di un ematoma subcoriale e la sua grandezza aumentano il rischio di aborto spontaneo nelle gravidanze con minaccia d'aborto, come anche vi può essere un aumento di complicanze della gravidanza, soprattutto rottura pretermine delle membrane , probabilmente poiché la raccolta di sangue, determina una placentazione anomala

The effects of subchorionic hematoma on pregnancy outcome in patients with threatened abortion

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Abstract

Objective: To assess the effects of ultrasonographically detected subchorionic hematomas on pregnancy outcomes in patients with vaginal bleeding within the first half of pregnancy.

Material and Methods: Patients diagnosed with threatened abortion due to painless vaginal bleeding and who were followed up in an in-patient service during the first vaginal bleeding between January 2009 and December 2010 were included in this retrospective cohort study. Patients were divided into two groups according to the presence of subchorionic hematoma. Miscarriage rates and pregnancy outcomes of ongoing pregnancies were compared between the groups.

Results: There were no statistically significant differences between the groups regarding demographic parameters, including age, parity, previous miscarriage history, and gestational age at first vaginal bleeding. While 13 of 44 pregnancies (29.5%) with subchorionic hematoma resulted in miscarriage, 25 of 198 pregnancies (12.6%) without subchorionic hematoma resulted in miscarriage (p=.010). The gestational age at miscarriage and the duration between first vaginal bleeding and miscarriage were similar between the groups. The outcome measures of ongoing pregnancies, such as gestational week at delivery, birth weight, and delivery route, were also similar between the groups.

Conclusion: Ultrasonographically detected subchorionic hematoma increases the risk of miscarriage in patients with vaginal bleeding and threatened abortion during the first 20 weeks of gestation. However, it does not affect the pregnancy outcome measures of ongoing pregnancies. (J Turk Ger Gynecol Assoc 2014; 15: 239-42)

Key words: Abortion, threatened, miscarriage, spontaneous, pregnancy outcome

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PROGNOS

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Pregnancy Outcome in Women with Threatened Miscarriage: a Year Study

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ORIGINAL PAPER

SUMMARY

Introduction: Patients with threatened miscarriage associated with adverse pregnancy outcomes because of associated pregnancy and labor complications. **Objectives:** To evaluate the effect of threatened miscarriage on early and late pregnancy outcome. **Methods:** A retrospective case –controlled study was performed on 89 women with threatened miscarriage (study group) at Maternity and Children Hospital Buraidah, KSA from January 2010 to December 2010. They were matched for age and parity to 45 cases (control group) attending route antenatal clinic at the same time. Data recorded included, demographic characteristics and detailed pregnancy outcome and ultrasound finding including gestational age, cardiac activity and subchorionic hematoma. **Results:** The overall adverse pregnancy outcome was significantly higher in the studied cases compared to the control group (p=015).The miscarriage rate was significantly higher in study group compared to the controls group, (16.9%vs 2.2%, p=0000). Preterm delivery, babies with low birth weight and premature rupture of membranes were significantly higher in the miscarriage group compared to the controls group, (15.7% vs 2.2%, p=0.001), (15.7% vs 2.2%), p=0.001) and (6.7%) vs 4.45), p=0.016). There were no significant differences in other pregnancy outcomes. **Conclusion:** threatened miscarriage is associated with increased incidence of adverse pregnancy outcome. The risk is specially increased in premature rupture of the membranes, preterm delivery and neonatal birth weight.

Key words: adverse pregnancy, threatened miscarriage, preterm delivery, neonatal birth weight.

TRATTAMENTO : prevenzione alloimmunizzazione - Controverso

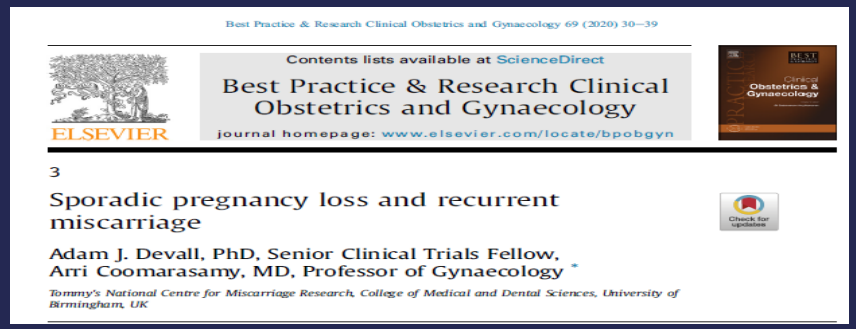
- È stato dimostrato che l'antigene D è presente sulla superficie dei globuli rossi fetali a partire dalla 7° settimana di gestazione e che 0.1mL di globuli rossi fetali sono sufficienti per determinare un'immunizzazione materna . Il parto rappresenta l'evento immunizzante anti D più frequente in caso di gravidanza Rh (D) negativo con feto Rh (D) positivo ma, anche durante la gestazione, si possono verificare emorragie feto-materne misconosciute potenzialmente immunizzanti. Nelle donne RH (D) negative non immunizzate è consigliata immunoprofilassi Rh al dosaggio di 300 µg al verificarsi delle seguenti condizioni che possono favorire il passaggio di eritrociti fetali nel circolo materno :
- Diagnosi prenatale invasiva (amniocentesi, funicolocentesi, villocentesi)
- Embrioriduzione di uno o più feti (IVG selettiva), terapia fetale (introduzione di shunt, trasfusione fetale intrauterina)
- Traumi addominali diretti, indiretti aperti o chiusi
- Emorragia ante partum
- Morte intrauterina fetale
- Rivolgimento fetale esterno
- Interruzione volontaria di gravidanza con metodi chirurgici e/o medici
- Aborto spontaneo completo o incompleto seguito da revisione strumentale della cavità uterina, indipendentemente dall'età gestazionale. Nell'aborto, in assenza di manovre traumatiche dell'utero o nelle perdite

- Nell'aborto, in assenza di manovre traumatiche dell'utero o nelle perdite ematiche durante il I trimestre di gravidanza, il rischio di immunizzazione è del 1,5-2 %. Le società scientifiche raccomandano la somministrazione di 120mcg di immunoglobuline anti-D prima delle 12 settimane e 300 mcg dopo le 12 settimane

TRATTAMENTO

- Nella minaccia d'aborto in realtà non vi sono terapie assodate che migliorino certamente l'Outcome della gravidanza, i dati scientifici anche sull'utilizzo del Progesterone sono controversi
- Spesso come primo approccio si consiglia il riposo, l'astensione dai rapporti sessuali, l'allontanamento da eventi stressanti, ma non vi è alcuna dimostrazione scientifica che tali astensioni determinino un outcome favorevole, soprattutto fino alla 8° settimana di gravidanza quando le cause di aborto spontaneo sono soprattutto genetiche
- La condotta d'attesa, l'utilizzo di antidolorifici , non FANS, e la raccomandazione di eseguire controlli ecografici scadenzati potrebbero essere il principale approccio
- TERAPIE????

PROGESTERONE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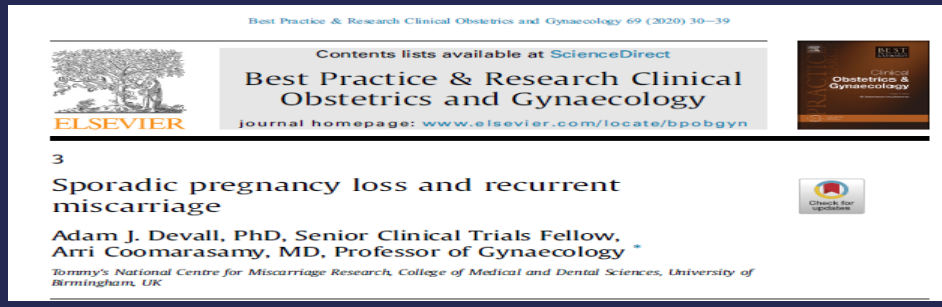
- Il progesterone è un ormone essenziale per lo stabilirsi, prepara l'endometrio a trasformarsi in deciduafavorendo l'impianto , ela prosecuzione della gravidanza
- Dai primi studi sui conigli nel 1910, in cui si scoprì che il progesterone prodotto dal corpo luteo era essenziale per il mantenimento della gravidanza, si è ipotizzato che il progesterone potesse avere un ruolo terapeutico anche nel mantenimento e nel prolungamento della gravidanza stessa, e quindi un suo uso terapeutico nell'aborto spontaneo e nella minaccia d'aborto
- Il Deficit della Fase Luteale (difetto di produzione di progesterone da parte del corpo luteo, con bassi livelli di ormone) si ipotizza sia una delle cause di aborto spontaneo euploide, in cui si pensa che una non adeguata produzione di progesterone da parte dell'ovaio sia il determinante della perdita fetale, ma anche qui i dati sulla certa esistenza di questa patologia non ci sono

PROGESTERONE



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- Si è tentato quindi di utilizzare il progesterone in virtù delle sue proprietà in due condizioni che aumentano il rischio di aborto: l'aborto spontaneo ricorrente e la minaccia d'aborto, soprattutto in quelle condizioni caratterizzate come aborti Euplodi , che aumentano all'aumentare del numero di aborti
- I dati dei vari studi presi in esame sarebbero a favore di un effetto positivo sull'esito favorevole della gravidanza della somministrazione di progesterone nelle gravide con aborto ricorrente

The largest and most recent trial conducted to date to examine the effect of progesterone supplementation for prevention of miscarriage in women with a history of recurrent miscarriage is the **PRO**gesterone in recurrent **MIS**carriag**E**s (PROMISE) Trial [31]. This is a large, a high-quality trial, with computer-generated third-party randomization, allocation concealment, double-blinding, placebo-control, excellent follow-up rate, and a pre-specified statistical analysis plan that was diligently implemented. A total of 836 women were randomized to the trial, and women were randomly assigned to receive either 400 mg of vaginal progesterone (Utrogestan®) twice daily or placebo from the time of positive pregnancy test up to 12 weeks of pregnancy or placebo. The primary outcome was live birth ≥24 weeks. The primary analysis of the PROMISE Trial found that the live birth rate was 66% (262/398) in the progesterone group versus 63% (271/428) in the placebo group (RR 1.04, 95% CI 0.94–1.15). There was a 3% higher live birth rate with progesterone, but the trial finding was reported as not statistically significant due to the large P value (P = 0.45) and the consequent statistical uncertainty. A pre-specified subgroup analysis was also performed by the number of previous miscarriages women had suffered; the study population was split into two subgroups—one included women who had 3 previous miscarriages, and the other included women who had ≥4 miscarriages. A subgroup analysis by 3, 4, 5 and ≥ 6 previous miscarriages was also performed for hypothesis generation to assess whether a biological gradient existed within these subgroups. The findings appeared to suggest a trend toward greater benefit with increasing number of previous miscarriages (Fig. 4). While the small sample sizes in the subgroups and the large P value for test of subgroup interaction (P = 0.41) suggested an inconclusive subgroup effect, the findings generated a hypothesis that a subgroup effect existed with a biological gradient related to the increasing number of previous miscarriages.

PROMISE TRIAL

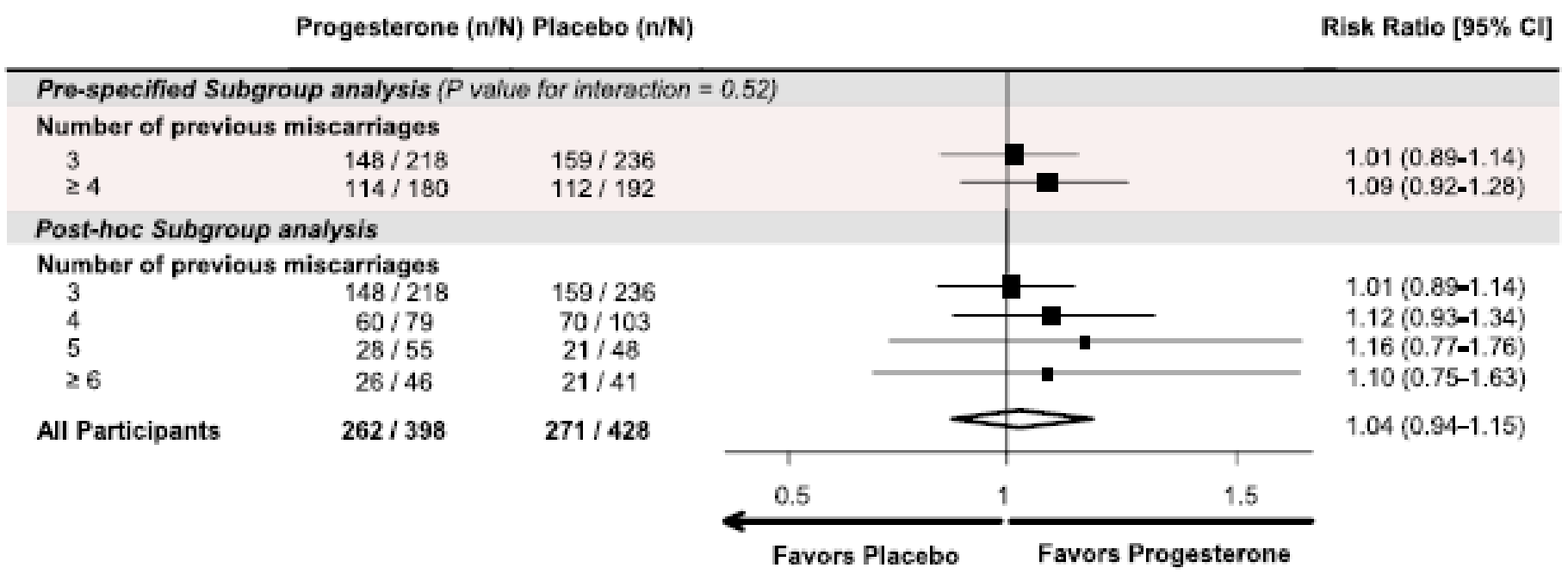
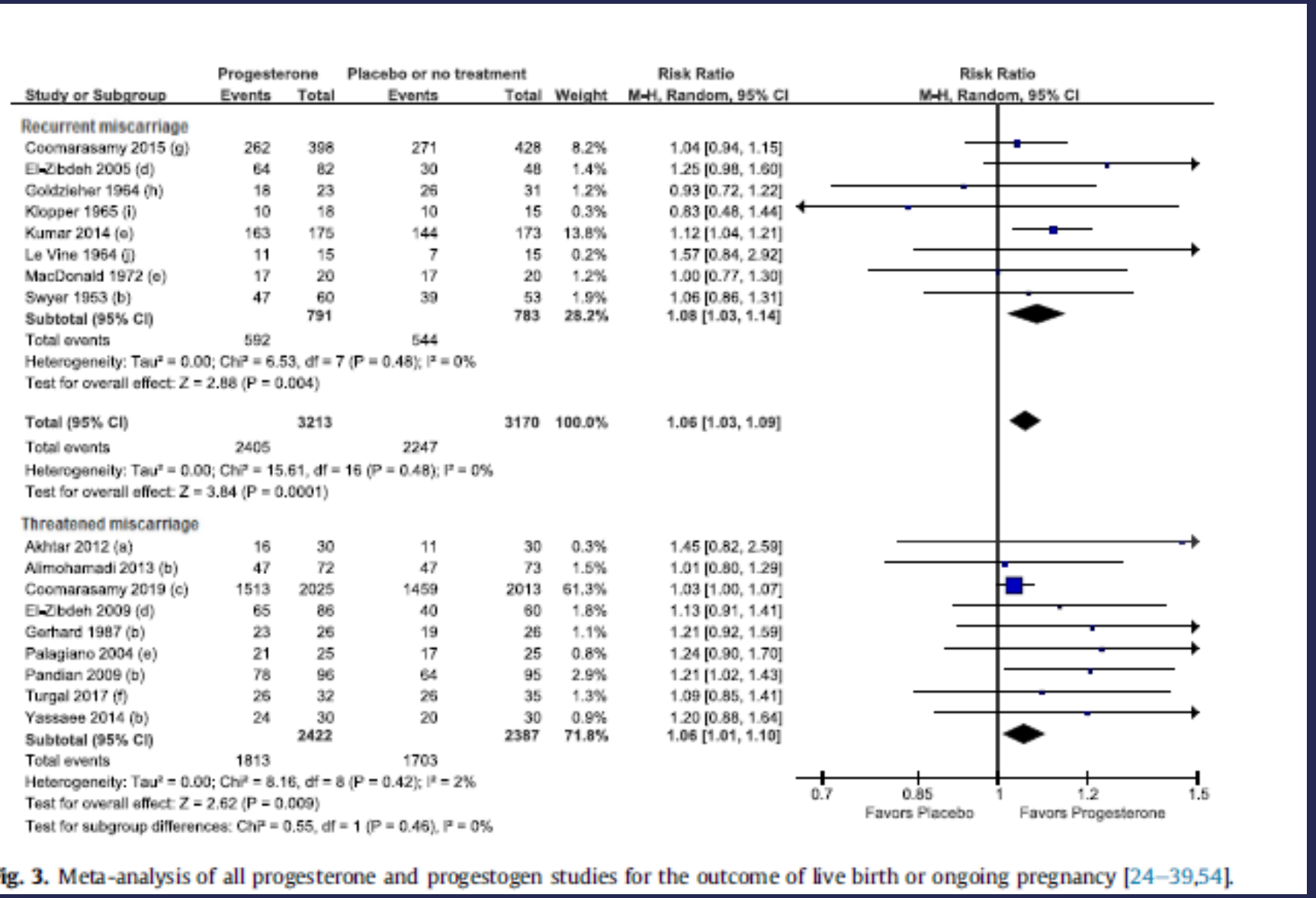


Fig. 4. PROMISE Trial subgroup analysis by number of previous miscarriages on the outcome of live birth >24 weeks.

PROGESTERONE



Study or Subgroup	Progesterone Events	Progesterone Total	Placebo or no treatment Events	Placebo or no treatment Total	Weight	Risk Ratio M-H, Random, 95% CI
Recurrent miscarriage						
Coomarasamy 2015 (g)	262	398	271	428	8.2%	1.04 [0.94, 1.15]
El-Zibdeh 2005 (d)	64	82	30	48	1.4%	1.25 [0.98, 1.60]
Goldzieher 1964 (h)	18	23	26	31	1.2%	0.93 [0.72, 1.22]
Klopper 1965 (i)	10	18	10	15	0.3%	0.83 [0.48, 1.44]
Kumar 2014 (e)	163	175	144	173	13.8%	1.12 [1.04, 1.21]
Le Vine 1964 (j)	11	15	7	15	0.2%	1.57 [0.84, 2.92]
MacDonald 1972 (e)	17	20	17	20	1.2%	1.00 [0.77, 1.30]
Swyer 1953 (b)	47	60	39	53	1.9%	1.06 [0.86, 1.31]
Subtotal (95% CI)		**791**		**783**	**28.2%**	**1.08 [1.03, 1.14]**
Total events	592		544			
Heterogeneity: Tau² = 0.00; Chi² = 6.53, df = 7 (P = 0.48); I² = 0%						
Test for overall effect: Z = 2.88 (P = 0.004)						
Total (95% CI)		**3213**		**3170**	**100.0%**	**1.06 [1.03, 1.09]**
Total events	2405		2247			
Heterogeneity: Tau² = 0.00; Chi² = 15.61, df = 16 (P = 0.48); I² = 0%						
Test for overall effect: Z = 3.84 (P = 0.0001)						
Threatened miscarriage						
Akhtar 2012 (a)	16	30	11	30	0.3%	1.45 [0.82, 2.59]
Alimohamadi 2013 (b)	47	72	47	73	1.5%	1.01 [0.80, 1.29]
Coomarasamy 2019 (c)	1513	2025	1459	2013	61.3%	1.03 [1.00, 1.07]
El-Zibdeh 2009 (d)	65	86	40	60	1.6%	1.13 [0.91, 1.41]
Gerhard 1987 (b)	23	26	19	26	1.1%	1.21 [0.92, 1.59]
Palagiano 2004 (e)	21	25	17	25	0.8%	1.24 [0.90, 1.70]
Pandian 2009 (b)	78	96	64	95	2.9%	1.21 [1.02, 1.43]
Turgal 2017 (f)	26	32	26	35	1.3%	1.09 [0.85, 1.41]
Yassaee 2014 (b)	24	30	20	30	0.9%	1.20 [0.88, 1.64]
Subtotal (95% CI)		**2422**		**2387**	**71.8%**	**1.06 [1.01, 1.10]**
Total events	1813		1703			
Heterogeneity: Tau² = 0.00; Chi² = 8.16, df = 8 (P = 0.42); I² = 2%						
Test for overall effect: Z = 2.62 (P = 0.009)						
Test for subgroup differences: Chi² = 0.55, df = 1 (P = 0.46), I² = 0%						

Fig. 3. Meta-analysis of all progesterone and progestogen studies for the outcome of live birth or ongoing pregnancy [24–39,54].

PROGESTERONE

- Nella metanalisi l'utilizzo del progesterone migliora l'Outcome della gravidanza nella minaccia d'aborto
- Il trial più importante è il PRISM trial che ha dimostrato che l'effetto positivo del progesterone era evidente soprattutto nelle gravide che soffrivano di aborto ricorrente , con un gradiente positivo: più aborti precedenti avessero avuto maggiore era l'effetto

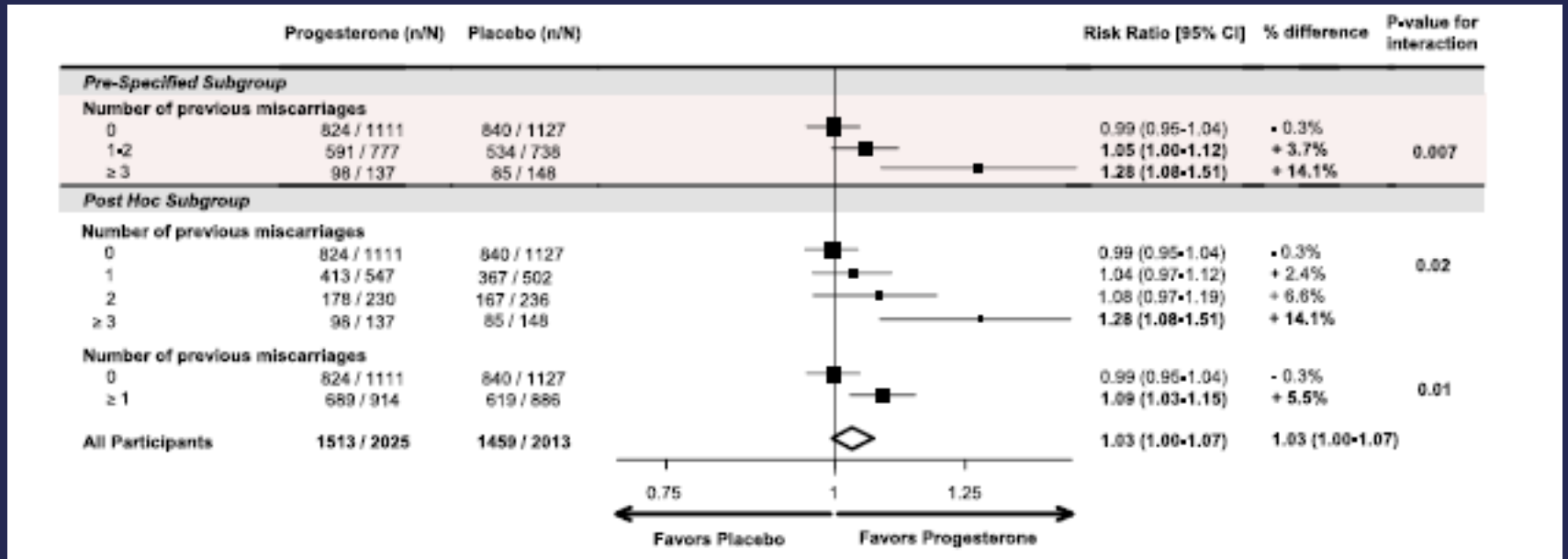


Fig. 5. PRISM Trial subgroup analysis by number of previous miscarriages on the outcome of live birth ≥34 weeks.

Sicurezza del Progesterone

- Nei due più grandi trial è stato utilizzato il progesterone micronizzato che ha un profilo di sicurezza maggiore di altri progestinici quali il diirdogestrone ed il 17 OH progesterone caproato, ed è quello consigliato

The use of steroid hormones in the first trimester is a serious issue as organogenesis takes place at this time, and therefore there is the possibility of harm of not only congenital anomalies, but also of long-term, and even inter-generational effects. Synthetic progestogens, which include dydrogesterone and 17-hydroxyprogesterone, have a different molecular structure, pharmacodynamics and pharmacokinetics, as well as a different safety profile [41–43]. It is worth noting that dydrogesterone is not currently a licenced drug in the UK or USA, and there are studies suggesting potential harm from this drug, particularly congenital heart disease [41]. Therefore, the findings from vaginal micronized progesterone are not generalizable to other synthetic progestogens.

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3

Sporadic pregnancy loss and recurrent miscarriage

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Tommy's National Centre for Miscarriage Research, College of Medical and Dental Sciences, University of Birmingham, UK

Implications for future research

Further research is required to enhance our understanding of LPD and develop and validate tests to identify women with LPD-related pregnancy losses. The increased effectiveness of progesterone with increasing number of miscarriages indicates that endometrial defects are a major driver of higher-order miscarriages. Yet, even after multiple miscarriages, the live birth rate and cumulative live birth rate in these patients remain high. Presumably, this means that the underlying endometrial defect is intermittent rather than persistent and that its frequency (i.e. number of 'normal' versus 'abnormal' cycles) determines the likelihood of miscarriage. This disease model is compatible with emerging biology demonstrating that tissue homeostasis in the cycling endometrium is dependent on recruitment of bone marrow-derived stem cells and uterine NK cells. Both 'homeostatic' mechanisms are perturbed in recurrent miscarriage [51–53]. A 'dynamic' disease model may help to explain the failure of current diagnostic approaches, such as screening for luteal phase defects.

Currently, we rely on clinical history to profile patients who may have a high risk of progesterone-related problem. However, this is imprecise. Accurate endometrial tests may allow more precise targeting of patients who may benefit from progesterone treatment. Karyotyping all pregnancy losses may also help to better risk-stratify women who may benefit from progesterone therapy; the role of routine karyotyping using modern genetic analysis needs further research, including the health economic implications of such an approach. Our research focused on first trimester use of progesterone; research is also needed to explore the effects of luteal phase progesterone use. Development and validation of tests, along with therapeutic trials to determine the efficacy of luteal phase progesterone and other potential interventions, are needed.

NICE guideline

Published: 17 April 2019

www.nice.org.uk/guidance/ng126

1.5 Management of miscarriage

Threatened miscarriage

1.5.1 Advise a woman with a confirmed intrauterine pregnancy with a fetal heartbeat who presents with vaginal bleeding, but has no history of previous miscarriage, that:

- if her bleeding gets worse, or persists beyond 14 days, she should return for further assessment
- if the bleeding stops, she should start or continue routine antenatal care. **[2012, amended 2021]**

1.5.2 Offer vaginal micronised progesterone 400 mg twice daily to women with an intrauterine pregnancy confirmed by a scan, if they have vaginal bleeding and have previously had a miscarriage. **[2021]**

1.5.3 If a fetal heartbeat is confirmed, continue progesterone until 16 completed weeks of pregnancy. **[2021]**

In November 2021, this was an off-label use of vaginal micronised progesterone. See NICE's information on prescribing medicines.

Cochrane Library

Cochrane Database of Systematic Reviews

Wahabi HA, Fayed AA, Esmaeil SA, Bahkali KH.
Progestogen for treating threatened miscarriage.
Cochrane Database of Systematic Reviews 2018, Issue 8. Art. No.: CD005943.
DOI: 10.1002/14651858.CD005943.pub5.

Progestogen for treating threatened miscarriage (Review)

Background

Miscarriage is a common complication encountered during pregnancy. It is defined as spontaneous pregnancy loss before 20 weeks' gestation. Progesterone's physiological role is to prepare the uterus for the implantation of the embryo, enhance uterine quiescence and suppress uterine contractions, hence, it may play a role in preventing rejection of the embryo. Inadequate secretion of progesterone in early pregnancy has been linked to the aetiology of miscarriage and progesterone supplementation has been used as a treatment for threatened miscarriage to prevent spontaneous pregnancy loss. This update of the Cochrane Review first published in 2007, and previously updated in 2011, investigates the evidence base for this practice.

Objectives

To determine the efficacy and the safety of progestogens in the treatment of threatened miscarriage.

Treatment of miscarriage with progestogens compared to placebo or no treatment probably reduces the risk of miscarriage; (risk ratio (RR) 0.64, 95% confidence interval (CI) 0.47 to 0.87; 7 trials; 696 women; moderate-quality evidence). Treatment with oral progestogen compared to no treatment also probably reduces the miscarriage rate (RR 0.57, 95% CI 0.38 to 0.85; 3 trials; 408 women; moderate-quality evidence). However treatment with vaginal progesterone compared to placebo, probably has little or no effect in reducing the miscarriage rate (RR 0.75, 95% CI 0.47 to 1.21; 4 trials; 288 women; moderate-quality evidence). The subgroup interaction test indicated no difference according to route of administration between the oral and vaginal subgroups of progesterone.

Treatment of miscarriage with the use of progestogens compared to placebo or no treatment may have little or no effect in reducing the rate of preterm birth (RR 0.86, 95% CI 0.52 to 1.44; 5 trials; 588 women; low-quality evidence).

We are uncertain if treatment of threatened miscarriage with progestogens compared to placebo or no treatment has any effect on the rate of congenital abnormalities because the quality of the evidence is very low (RR 0.70, 95% CI 0.10 to 4.82; 2 trials; 337 infants; very-low quality evidence).

Authors' conclusions

The results of this Cochrane Review suggest that progestogens are probably effective in the treatment of threatened miscarriage but may have little or no effect in the rate of preterm birth. The evidence on congenital abnormalities is uncertain, because the quality of the evidence for this outcome was based on only two small trials with very few events and was found to be of very low quality.

Micronized vaginal progesterone to prevent miscarriage: a critical evaluation of randomized evidence

Arri Coomarasamy, MD, MRCOG; Adam J. Devall, PhD; Jan J. Brosens, PhD; Siobhan Quenby, MD, FRCOG; Mary D. Stephenson, MD; Sony Sierra, MD; Ole B. Christiansen, MD; Rachel Small, BSc; Jane Brewin, BSc; Tracy E. Roberts, PhD; Rima Dhillon-Smith, PhD, MRCOG; Hoda Harb, PhD; Hannah Noordali, PhD; Argyro Papadopoulou, BSc; Abey Eapen, PhD, MBBS; Matt Prior, MRCOG; Gian Carlo Di Renzo, MD; Kim Hinshaw, MBBS, FRCOG; Ben W. Mol, MD, PhD; Mary Ann Lumsden, MD, FRCOG; Yacoub Khalaf, MD, FRCOG; Andrew Shennan, MD, FRCOG; Mariette Goddijn, MD, PhD; Madelon van Wely, PhD; Maya Al-Memar, PhD, MRCOG; Phil Bennett, PhD, FRCOG; Tom Bourne, PhD, FRCOG; Raj Rai, MD, MRCOG; Lesley Regan, MD, FRCOG; Ioannis D. Gallos, MD, MRCOG

Progesterone is essential for the maintenance of pregnancy. Several small trials have suggested that progesterone supplementation may reduce the risk of miscarriage in women with recurrent or threatened miscarriage. Cochrane Reviews summarized the evidence and found that the trials were small with substantial methodologic weaknesses. Since then, the effects of first-trimester use of vaginal micronized progesterone have been evaluated in 2 large, high-quality, multicenter placebo-controlled trials, one targeting women with unexplained recurrent miscarriages (the PROMISE [PROgesterone in recurrent MIScarriagE] trial) and the other targeting women with early pregnancy bleeding (the PRISM [PRogesterone In Spontaneous Miscarriage] trial). The PROMISE trial studied 836 women from 45 hospitals in the United Kingdom and the Netherlands and found a 3% greater live birth rate with progesterone but with substantial statistical uncertainty. The PRISM trial studied 4153 women from 48 hospitals in the United Kingdom and found a 3% greater live birth rate with progesterone, but with a *P* value of .08. A key finding, first observed in the PROMISE trial, and then replicated in the PRISM trial, was that treatment with vaginal micronized progesterone 400 mg twice daily was associated with increasing live birth rates according to the number of previous miscarriages. Pre-specified PRISM trial subgroup analysis in women with the dual risk factors of previous miscarriage(s) and current pregnancy bleeding fulfilled all 11 conditions for credible subgroup analysis. For the subgroup of women with a history of 1 or more miscarriage(s) and current pregnancy bleeding, the live birth rate was 75% (689/914) with progesterone vs 70% (619/886) with placebo (rate difference 5%; risk ratio, 1.09, 95% confidence interval, 1.03—1.15; *P*=.003). The benefit was greater for the subgroup of women with 3 or more previous miscarriages and current pregnancy bleeding; live birth rate was 72% (98/137) with progesterone vs 57% (85/148) with placebo (rate difference 15%; risk ratio, 1.28, 95% confidence interval, 1.08—1.51; *P*=.004). No short-term safety concerns were identified from the PROMISE and PRISM trials. Therefore, women with a history of miscarriage who present with bleeding in early pregnancy may benefit from the use of vaginal micronized progesterone 400 mg twice daily. Women and their care providers should use the findings for shared decision-making.

Key words: bleeding, luteal phase deficiency, meta-analysis, recurrent miscarriage, threatened miscarriage, vaginal micronized progesterone

REVIEW Open Access

Pregnancy-related complications and perinatal outcomes following progesterone supplementation before 20 weeks of pregnancy in spontaneously achieved singleton pregnancies: a systematic review and meta-analysis

Hanglin Wu[1], Songying Zhang[2], Xiaona Lin[2], Jing He[1], Shasha Wang[2] and Ping Zhou[2*]

Abstract

Background: Progesterone supplementation is widely performed in women with threatened miscarriage or a history of recurrent miscarriage; however, the effects of early progesterone supplementation on pregnancy-related complications and perinatal outcomes in later gestational weeks remain unknown.

Methods: Ovid MEDLINE, the Cochrane Library, Embase and ClinicalTrials.gov were searched until April 3rd, 2021. Randomized controlled trials regarding spontaneously achieved singleton pregnancies who were treated with progestogen before 20 weeks of pregnancy and were compared with those women in unexposed control groups were selected for inclusion. We performed pairwise meta-analyses with the random-effects model. The risk of bias was assessed according to the Cochrane Collaboration tool. The primary outcomes included preeclampsia (PE), and gestational diabetes mellitus (GDM), with the results presented as odds ratios (ORs) with 95% confidence intervals (CIs).

Results: We identified nine eligible studies involving 6439 participants. The pooled OR of subsequent PE following early progestogen supplementation was 0.64 (95% CI 0.42–0.98, moderate quality of evidence). A lower OR for PE was observed in the progestogen group when the subgroup analysis was performed in the vaginal subgroup (OR 0.62, 95%CI 0.40–0.96). There was insufficient evidence of a difference in the rate of GDM between pregnant women with early progestogen supplementation and unexposed pregnant women (OR 1.02, 95% CI 0.79–1.32, low quality of evidence). The pooled OR of low birth weight (LBW) following oral dydrogesterone was 0.57 (95% CI 0.34–0.95, moderate quality of evidence). The results were affected by a single study and the total sample size of enrolled women did not reach the required information size.

Conclusion: Use of vaginal micronized progesterone (Utrogestan) in spontaneously achieved singleton pregnancies with threatened miscarriage before 20 weeks of pregnancy may reduce the risk of PE in later gestational weeks.

Use of Oral Progestogen in Women With Threatened Miscarriage in the First Trimester
A Randomized Double-blind Controlled Trial

Diana Man Ka Chan; Ka Wang Cheung; Jennifer Ka Yee Ko; Sofie Shuk Fei Yung; Shui Fan Lai; Mei Ting Lam; Dorothy Yuet Tao Ng; Vivian Chi Yan Lee; Raymond Hang Wun Li; Ernest Hung Yu Ng

Hum Reprod. 2021;36(3):587-595.

- **Abstract**
- **Study Question:** Will use of oral progestogen in women with threatened miscarriage in the first trimester reduce the miscarriage rate when compared with placebo?
- **Summary Answer:** Use of oral progestogen in women with threatened miscarriage in the first trimester did not reduce miscarriage before 20 weeks when compared with placebo.
- **What is Known Already:** Miscarriage is a common complication of pregnancy and occurs in 15–20% of clinically recognized pregnancies. Use of vaginal progestogens is not effective in reducing miscarriage but there is still no good evidence to support use of oral progestogen for the treatment of threatened miscarriage.
- **Study Design, Size, Duration:** This was a randomized double-blind controlled trial. A total of 406 women presenting with threatened miscarriage in the first trimester were recruited from 30 March 2016 to May 2018.
- **Participants/Materials, Setting, Methods:** Women attending Early Pregnancy Assessment Clinics because of vaginal bleeding during the first trimester were recruited and randomly assigned to use dydrogesterone 40 mg orally, followed by 10 mg orally three times a day or placebo until 12 completed weeks of gestation or 1 week after the bleeding stopped, whichever was later. The primary outcome was the miscarriage rate before 20 weeks of gestation.
- **Main Results and the Role of Chance:** The two groups of women had comparable age, BMI, number of previous miscarriages, gestation and ultrasound findings at presentation. The miscarriage rate before 20 weeks of gestation was similar in both groups, being 12.8% (26/203) in the progestogen group and 14.3% (29/203) in the placebo group (relative risk 0.897, 95% CI 0.548–1.467; $P = 0.772$). The live birth rate was 81.3% in the progestogen group versus 83.3% in the placebo group ($P = 0.697$). No significant differences were found between the two groups in terms of obstetric outcomes and side effects.
- **Limitations, Reasons for Caution:** The primary outcome was the miscarriage rate, rather than the live birth rate. Women were recruited from Early Pregnancy Assessment Clinics and those with heavy vaginal bleeding might be admitted into wards directly instead of attending Early Pregnancy Assessment Clinic. The severity of vaginal bleeding was subjectively graded by women themselves. The sample size was not adequate to demonstrate a smaller difference in the miscarriage rate between the progestogen and placebo groups. We did not exclude women with multiple pregnancy, which increased the risk of miscarriage although there was only one set of twin pregnancy in the placebo group.
- **Wider Implications of the Findings:** Use of oral progestogen is not recommended in women with threatened miscarriage in the first trimester.
- **Study Funding/Competing Interest(S):** This study was funded by the Health and Medical Research Fund, HKSAR (reference number 12132341). All authors declared no conflict of interest.
- **Trial Registration Number:** ClinicalTrials.gov with an identifier NCT02128685.
- **Trial Registration Date:** 1 May 2014.

MULTIVITAMINICI

Cochrane Library

Cochrane Database of Systematic Reviews

Vitamin supplementation for preventing miscarriage (Review)

Balogun OO, da Silva Lopes K, Ota E, Takemoto Y, Rumbold A, Takegata M, Mori R.
Vitamin supplementation for preventing miscarriage.
Cochrane Database of Systematic Reviews 2016, Issue 5. Art. No.: CD004073.
DOI: 10.1002/14651858.CD004073.pub4.

Vitamin A supplementation

No difference was found in the risk of total fetal loss (RR 1.01, 95% CI 0.61 to 1.66, three trials, 1640 women; *low-quality evidence*); early or late miscarriage (RR 0.86, 95% CI 0.46 to 1.62, two trials, 1397 women; *low-quality evidence*) or stillbirth (RR 1.29, 95% CI 0.57 to 2.91, three trials, 1640 women; *low-quality evidence*) between women receiving vitamin A plus iron and folate compared with placebo or no vitamin A groups. There was no evidence of differences in the risk of total fetal loss or miscarriage between women receiving any other combination of vitamin A compared with placebo or no vitamin A groups.

Multivitamin supplementation

There was evidence of a decrease in the risk for stillbirth among women receiving multivitamins plus iron and folic acid compared iron and folate only groups (RR 0.92, 95% CI 0.85 to 0.99, 10 trials, 79,851 women; *high-quality evidence*). Although total fetal loss was lower in women who were given multivitamins without folic acid (RR 0.49, 95% CI 0.34 to 0.70, one trial, 907 women); and multivitamins with or without vitamin A (RR 0.60, 95% CI 0.39 to 0.92, one trial, 1074 women), these findings included one trial each with small numbers of women involved. Also, they include studies where the comparison groups included women receiving either vitamin A or placebo, and thus require caution in interpretation.

We found no difference in the risk of total fetal loss (RR 0.96, 95% CI 0.93 to 1.00, 10 trials, 94,948 women; *high-quality evidence*) or early or late miscarriage (RR 0.98, 95% CI 0.94 to 1.03, 10 trials, 94,948 women; *moderate-quality evidence*) between women receiving multivitamins plus iron and folic acid compared with iron and folate only groups.

There was no evidence of differences in the risk of total fetal loss or miscarriage between women receiving any other combination of multivitamins compared with placebo, folic acid or vitamin A groups.

Folic acid supplementation

There was no evidence of any difference in the risk of total fetal loss, early or late miscarriage, stillbirth or congenital malformations between women supplemented with folic acid with or without multivitamins and/or iron compared with no folic acid groups.

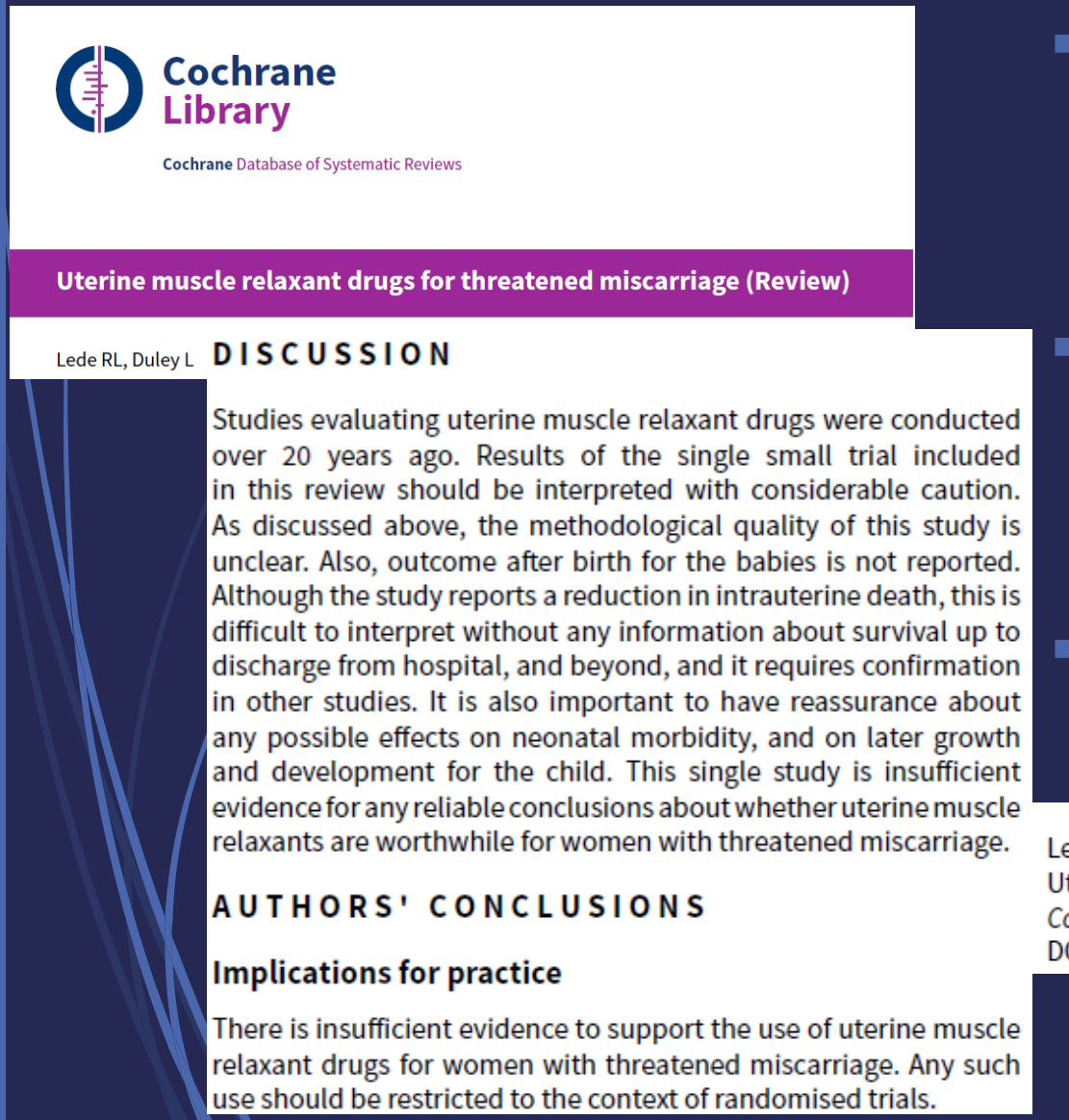
Antioxidant vitamins supplementation

There was no evidence of differences in early or late miscarriage between women given antioxidant compared with the low antioxidant group (RR 1.12, 95% CI 0.24 to 5.29, one trial, 110 women).

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.

TOCOLITICI ANTISPASTICI



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Uterine muscle relaxant drugs for threatened miscarriage (Review)

Lede RL, Duley L

DISCUSSION

Studies evaluating uterine muscle relaxant drugs were conducted over 20 years ago. Results of the single small trial included in this review should be interpreted with considerable caution. As discussed above, the methodological quality of this study is unclear. Also, outcome after birth for the babies is not reported. Although the study reports a reduction in intrauterine death, this is difficult to interpret without any information about survival up to discharge from hospital, and beyond, and it requires confirmation in other studies. It is also important to have reassurance about any possible effects on neonatal morbidity, and on later growth and development for the child. This single study is insufficient evidence for any reliable conclusions about whether uterine muscle relaxants are worthwhile for women with threatened miscarriage.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence to support the use of uterine muscle relaxant drugs for women with threatened miscarriage. Any such use should be restricted to the context of randomised trials.

- Alla minaccia d'aborto è stata spesso correlata un'aumentata contrattilità uterina, anche se non è chiaro se essa sia una causa od una conseguenza degli eventi che determinano la minaccia (ES il sanginamento)
- Isossisuprina, ritodrina e salbutamolo come beta 2 agonisti agiscono sulla muscolatura miometriale inibendone la contrazione, ma hanno comunque effetti collaterali importanti ed il loro uso per via orale pare comunque di poca utilità
- Gli spasmolitici invece vengono usati per ridurre la contrattilità della muscolatura liscia per il trattamento di coliche intestinali biliari e

Lede RL, Duley L.
Uterine muscle relaxant drugs for threatened miscarriage.
Cochrane Database of Systematic Reviews 2005, Issue 3. Art. No.: CD002857.
DOI: 10.1002/14651858.CD002857.pub2.

Reproductive BioMedicine Online (2016) 32, 362–376

REVIEW

The effect of peri-implantation administration of uterine relaxing agents in assisted reproduction treatment cycles: a systematic review and meta-analysis

Mohammed Khairy [a,*], Rima K Dhillon [b,c], Justin Chu [b,c], Madhurima Rajkhowa [a], Arri Coomarasamy [b,c]

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* Corresponding author. E-mail address: mohammed.mahmoud@bwnft.nhs.uk (M Khairy).

Abstract Sub-endometrial junctional zone peristalsis is increased by ovarian stimulation and traumatic embryo transfer, and is linked with decreased implantation and pregnancy rates in assisted reproduction treatments. Various agents have been used to inhibit uterine hyper-peristalsis at the time of embryo transfer with conflicting results. This systematic review aimed to identify if uterine relaxants administered in the peri-implantation period during assisted reproduction treatments could improve pregnancy outcomes through literature search with no language restrictions. The review reports on 3546 patients in 17 randomized controlled trials published between

The use of oral or transdermal agents is generally more appealing to patients and clinicians. In this review, the only oral agent that showed a significant effect on clinical pregnancy was the anticholinergic agent, hyoscine. This was, however, based on single clinical trial, which included a relatively small number of patients with low quality assessment grading and no reporting on the primary outcome of live birth rate (Zargar et al., 2013). Another small trial showed improvement of biochemical pregnancy rate with hyoscine but no clear data on clinical pregnancy rate (Sohrabvand et al., 2009). Therefore, caution must be taken when drawing any definitive conclusions for the use of these agents in routine clinical practice.

No statistically significant effect was found on live birth or clinical pregnancy from meta-analyses of other oral or transdermal agents. In the only RCT that exclusively included patients with recurrent implantation failure, however, a statistically significant effect was reported on clinical and ongoing pregnancy rate in the treatment arm using ritodrine (Tsirigotis et al., 2000).

In conclusion, insufficient evidence is currently avaailble to support the use of uterine relaxant agents around the time of embryo transfer in routine clinical practice. Given the methodological short comings of the current evidence, however, larger robust RCTs are clearly needed to investigate the usefulness of these agents if any (in particular, anticholinergic agents, oxytocin receptor antagonists and calcium channel blockers). It is possible that careful patient selection for the use of these agents might show greater benefit in future RCTs, e.g. patients who reported pain after previous embryo transfer, those where difficult embryo transfer is anticipated or patients with adenomyosis/endometriosis. With better scanning techniques and equipment, uterine hyper-peristalsis might be more readily detectable. This would allow the improved identification of patients who might benefit from these agents.

RIPOSO A LETTO

Inoltre il riposo a letto, aumenta il rischio di altre complicazioni quali tromboembolie venose ed embolia polmonare

Walsh CA. Maternal activity restriction to reduce preterm birth: Time to put this fallacy to bed. Aust N Z J Obstet Gynaecol. 2020 Oct;60(5):813-815. doi: 10.1111/ajo.13212. Epub 2020 Jul 20. PMID: 32691407.

Abstract

Activity restriction has traditionally been recommended to pregnant women, especially high-risk patients, to reduce preterm birth. However, there is no scientific evidence that bed-rest reduces preterm birth and, in many studies, women on bed-rest had higher rates of delivering preterm. Bed-rest in pregnancy is associated with significant physiological and psychosocial sequelae and reduced neonatal birth weight and be cannot be endorsed, even in women with a short cervix. The practice of prescribing bed-rest in pregnancy is outdated and should be abandoned.

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Cochrane Database of Systematic Reviews

Bed rest during pregnancy for preventing miscarriage (Review)

Aleman A, Althabe F, Belizán JM, Bergel E.
Bed rest during pregnancy for preventing miscarriage.
Cochrane Database of Systematic Reviews 2005, Issue 2. Art. No.: CD003576.
DOI: 10.1002/14651858.CD003576.pub2.

Main results

Only two studies including 84 women were identified. There was no statistically significant difference in the risk of miscarriage in the bed rest group versus the no bed rest group (placebo or other treatment) (risk ratio (RR) 1.54, 95% confidence interval (CI) 0.92 to 2.58). Neither bed rest in hospital nor bed rest at home showed a significant difference in the prevention of miscarriage. There was a higher risk of miscarriage in those women in the bed rest group than in those in the human chorionic gonadotrophin therapy group with no bed rest (RR 2.50, 95% CI 1.22 to 5.11). It seems that the small number of participants included in these studies is a main factor to make this analysis inconclusive.

Authors' conclusions

There is insufficient evidence of high quality that supports a policy of bed rest in order to prevent miscarriage in women with confirmed fetal viability and vaginal bleeding in first half of pregnancy.

STRESS OSSIDATIVO E ABORTO

Int J Clin Exp Med 2014;7(8):2179-2184
www.ijcem.com /ISSN:1940-5901/IJCEM0000950

Original Article

Changes in reactive oxygen species, superoxide dismutase, and hypoxia-inducible factor-1α levels in missed abortion

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Department of Gynecology and Obstetrics, The Fifth Hospital of Shanghai Affiliated to Fudan University, Shanghai 200240, China

Received May 30, 2014; Accepted June 14, 2014; Epub August 15, 2014; Published August 30, 2014

Table 2. Mean with standard deviation ROS, SOD, and HIF-1α levels in missed abortion and early pregnancy control groups

Group	n	ROS fluorescence intensity	SOD enzyme activity unit (U/mg prot)	HIF-1α (mg/ml)
Missed abortion	28	758.41 ± 86.48	0.43 ± 0.22	0.38 ± 0.05
Early pregnancy	35	445.84 ± 70.12	1.39 ± 0.49	1.62 ± 0.25

Studio di confronto fra i livelli di stress ossidativo (ROS), i livelli di antiossidanti (SOD) ed i livelli di HIF-1α (fattore di trascrizione che regola le risposte adattative all'ipossia) nei trofoblasti di pazienti con aborto spontaneo idiopatico (N=28) e pazienti con aborto indotto (N=32).

I livelli di stress ossidativo sono risultati aumentati nei trofoblasti di donne con aborto spontaneo idiopatico. I trofoblasti delle pazienti con aborto spontaneo hanno evidenziato anche una bassa presenza di antiossidanti endogeni e di HIF-1α.

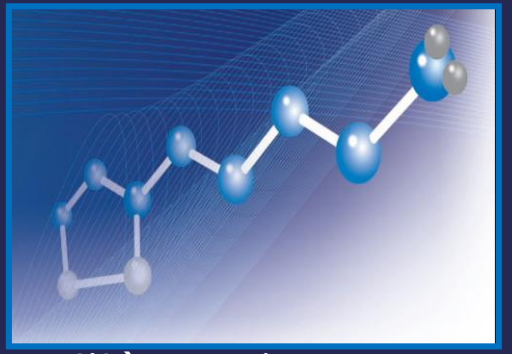
STRESS OSSIDATIVO E ABORTO SPONTANEO

Our study showed that the ROS and HIF-1α levels were inversely correlated in both the missed abortion and control groups. This finding suggests that lower HIF-1α availability is associated with higher ROS levels, and it supports the notion that ROS have an inhibitory action on HIF-1α. Our results are consistent with a pathogenesis of missed abortion involving three aspects. First, ROS may cause lipid peroxidation damage to embryos. The generated oxygen radicals may attack the combined HIF-1α and hypoxia response element (HRE) sites, such that HIF-1α cannot bind HRE to promote the transcription of genes downstream of the HRE elements. Second, increased ROS levels might change the partial pressure of oxygen in embryonic cells. In a hyperoxic environment, HIF-1α is gradually degraded, resulting in low levels of HIF-1α. Third, when their development has been incomplete, embryonic trophoblasts enter a cycle of ischemia and reperfusion prematurely, causing ischemic reperfusion damage to the embryo, which then, in a vicious cycle, produces even more ROS.

I ROS sono coinvolti nella patogenesi dell'aborto spontaneo perché:

1 – causano perossidazione lipidica delle cellule dell'embrione
2 – riducono le concentrazioni di HIF-1α e di conseguenza la capacità di adattamento alle condizioni di ipossia
3 – come conseguenza del punto precedente, il trofoblasto entra in un processo di ischemia-riperfusione che danneggia l'embrione, aumentando ulteriormente i livelli di stress ossidativo

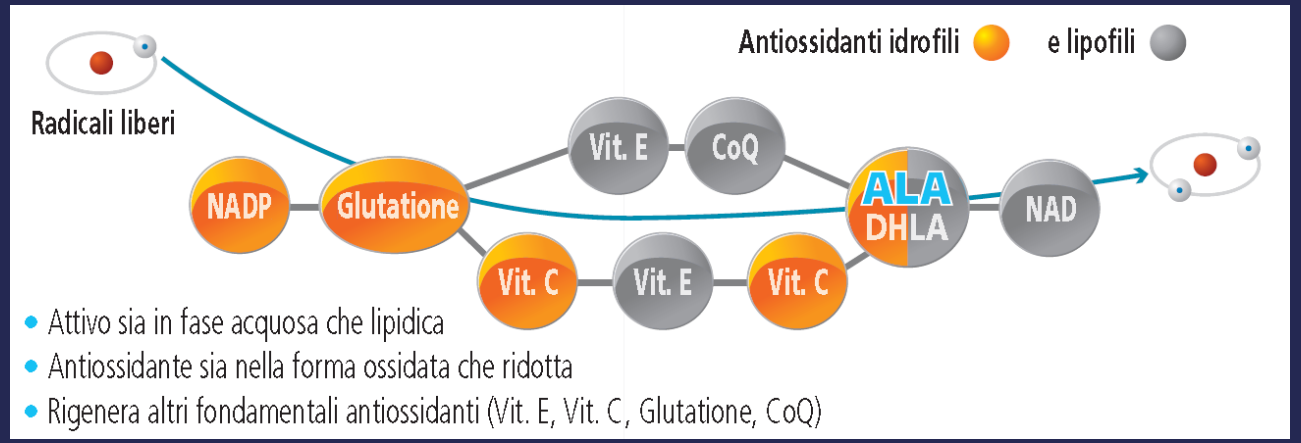
ACIDO LIPOICO (ALA)



- Presente nel nostro organismo anche se in piccole quantità, veniva considerato un elemento vitamino- simile, da alcuni

  è chiamato **vitamina N**.

- In realtà non è una vitamina; ne sono ricchi alimenti di origine animale
- Appartiene al gruppo degli **antiossidanti endogeni** (presenti naturalmente nel nostro organismo) ed ha diverse proprietà farmacologiche:
  - **antiossidante**
  - **pro-energetica**
  - **antinfiammatoria**
  - **immunomodulante**
  - **neurotrofica**
  - **insulino-simile**



ACIDO ALFA LIPOI

EXPERIMENTAL AND THERAPEUTIC MEDICINE 22: 1232, 2021

Benefits of α-lipoic acid in high-risk pregnancies (Review)

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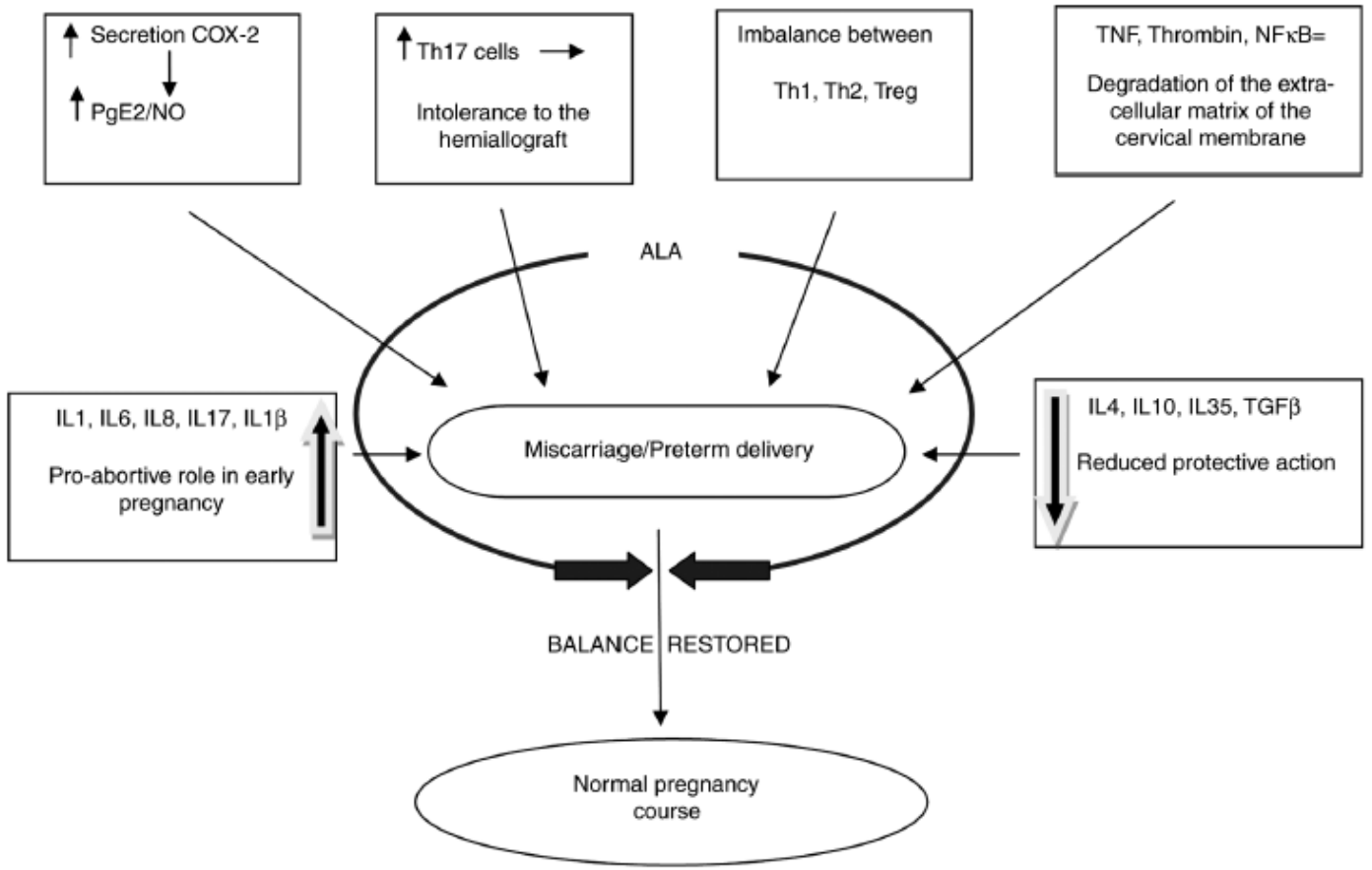
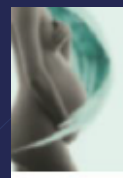


Figure 1. Schematic illustration of the role of specific cytokines, growth factors, chemokines and helper T cells in the etiopathogenesis of miscarriage and preterm delivery. ALA, α-lipoic acid; COX, cyclooxygenase; Pg, prostaglandin; NO, nitric oxide; Th, T helper; Treg, regulatory T cell.

4. Conclusions

ALA/DHLA acts as potent immunomodulatory redox couple, with a specific role in preventing miscarriage and premature delivery. The administration of ALA may represent a promising therapeutic strategy in several obstetric pathologies, such as complicated pregnancies with abnormal placentation/exaggerated maternal vascular inflammatory response (15), or hypoxia/perinatal ischemia caused by various factors (64). Validation of this therapeutic indication requires further studies. The onset of hypoxic or ischemic injury should be diagnosed accurately to determine the appropriate timing and dose for ALA administration.

ACIDO ALFA LIPOICO



European Review for Medical and Pharmacological Sciences 2015; 19: 3426-3432

Alpha Lipoic Acid (ALA) effects on subchorionic hematoma: preliminary clinical results

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PATIENTS AND METHODS: Nineteen pregnant women in the first trimester of gestation, with threatened miscarriage and ultrasound evidence of subchorionic hematoma, were included in the trial and randomly divided in two groups: controls, treated with 400 mg Progesterone (200 mg 2 times per day), given by vaginal suppositories, and case study treated with the same Progesterone dosage, plus ALA, given orally at the dose of 600 mg (300 mg 2 times per day, DAV®, Lo.Li. Pharma srl, Italy). Sixteen patients completed the trial. Treatment was performed until complete resolution of the clinical picture.

RESULTS: In both groups, the subjects improved significantly but, in general, a better and faster evolution in the major signs of threatened miscarriage was observed in the subjects treated with ALA and Progesterone. In these patients, the speed of resorption of subchorionic hematoma was significantly ($p \leq 0.05$) superior compared to controls. The ALA and Progesterone group showed a faster decrease or disappearance of all symptoms than that observed in the control group, however the difference was not significant.

CONCLUSIONS: These preliminary results suggest that ALA supplementation significantly contributes to speed up the process of restoration of physiological conditions in threatened miscarriage and ameliorates the medical conditions of both the mothers and the foetus, probably modulating the networks of cytokines, growth factors and other molecules.

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Resolution of subchorionic hematoma and symptoms of threatened miscarriage using vaginal alpha lipoic acid or progesterone: clinical evidences

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Abstract. – OBJECTIVE: Alpha Lipoic Acid (ALA) is a safe natural molecule that exerts a selective immunomodulating activity with antioxidant and anti-inflammatory properties. This randomized controlled clinical trial (RCT) tested the effect of the vaginal administration with ALA or Progesterone, in subchorionic hematoma resorption in women with threatened miscarriage.

PATIENTS AND METHODS: 400 mg of vaginal Progesterone or 10 mg of vaginal ALA were administered to sixty-two pregnant women, in the first trimester of gestation with threatened miscarriage and subchorionic hematoma. Controls were patients who chose not to receive any treatment.

RESULTS: In the ALA group the subchorionic hematoma was reabsorbed more quickly in comparison with the progression detected in Progesterone group ($p \leq 0.05$). The other parameters checked (pelvic pain and vaginal bleeding) did not show any significant difference and a smaller number of miscarriages was recorded in the ALA group, compared to Progesterone group.

CONCLUSIONS: Our data provides the first evidence of the efficacy of ALA, administered by vaginal route, in the healing process of patients with threatened miscarriage, thus supporting the normal course of pregnancy. Clinical trial registration number: NCT02601898 (ClinicalTrials.gov registry).

ACIDO ALFA LIPOICO

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Safety of oral alpha-lipoic acid treatment in pregnant women: a retrospective observational study

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Abstract. – **OBJECTIVE:** Alpha-lipoic acid is a natural molecule, which directly or by means of its reduced form, dihydrolipoic acid, exerts antioxidant, anti-inflammatory and immunomodulatory activities, very helpful also in preventing miscarriage and preterm delivery. Used as dietary supplement alpha-lipoic acid was demonstrated to be safe for living organisms even when administered at high doses. However, no study was made so far to verify the safety of its continuous administration on a substantial number of pregnant women. The present investigation was performed to answer this issue.

PATIENTS AND METHODS: An observational retrospective study was carried out analyzing 610 expectant mothers. They had been treated daily by oral route with 600 mg alpha-lipoic acid, for at least 7 weeks during gestation. The primary outcome was to verify alpha-lipoic acid safety in the mother and infant. Maternal safety was assessed by monitoring for adverse reactions, physical and clinical examination, including a morbidity assessment. Laboratory and clinical examinations were performed monthly. Neonatal safety was assessed by the evaluation of birth weight, gestational age, Apgar scores, neonatal death with the related cause of death. Data collected from the Birth Registry of Campania Region were used as control.

RESULTS: This study provided a very clear and reassuring picture about the safety of alpha-lipoic acid oral treatment during pregnancy. No adverse effect was noticed in mothers or newborns. The two sets of monitored data, from treated and controls, were completely superimposable or, in some cases, better in alpha-lipoic acid group.

CONCLUSIONS: Our results open a reassuring scenario regarding the administration of alpha-lipoic acid during pregnancy.

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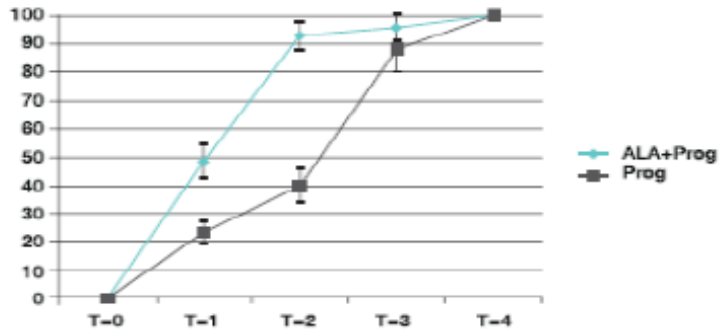

Fig. 8a: Progresso nel riassorbimento dell'ematoma (Δ percentuale della media ± ES), rilevato ecograficamente a tempi diversi di trattamento.
Nel gruppo ALA + Progesterone n = 9 e nel gruppo Progesterone n = 7.

I risultati indicano che i pazienti trattati con ALA più progesterone hanno avuto una migliore e più rapida evoluzione dei segni clinici e dei sintomi relativi alla minaccia di aborto. Il monitoraggio della risoluzione dell'ematoma, e delle modifiche nel sanguinamento vaginale, dolori addominali, utero morbido e contrazioni uterine, ha dimostrato che tutti i segni e i sintomi (tranne l'utero morbido) sono diminuiti o scomparsi nel gruppo trattato con ALA più progesterone, prima che nei controlli (progesterone da solo). Infatti, nonostante i trattamenti abbiano ottenuto risultati comparabili nella risoluzione delle contrazioni uterine, i risultati relativi ai sintomi soggettivi hanno evidenziato che i pazienti del gruppo ALA più progesterone hanno mostrato una più rapida risoluzione dei sintomi, migliorando nettamente la qualità della vita delle donne in gravidanza.

LATTOFERRINA

Vaginal Lactoferrin Administration Decreases Oxidative Stress in the Amniotic Fluid of Pregnant Women: An Open-Label Randomized Pilot Study

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Background: Oxidative stress (OxS) has been linked to several pregnancy-related complications. Previous studies demonstrated that lactoferrin (LF) has the ability to modulate inflammation, OxS and the immune function. Therefore, we aimed to observe whether vaginal LF administration was able to decrease OxS in the amniotic fluid (AF) of pregnant women undergoing mid-trimester genetic amniocentesis.

Methods: In this open-label clinical study, 60 pregnant women were divided into three groups: CONTROLS ($n = 20$), not treated with LF; LACTO 4HRS ($n = 20$), treated with LF 4 h prior to amniocentesis; LACTO 12HRS ($n = 20$), treated with LF 12 h prior to amniocentesis. Thiobarbituric acid reactive substances (TBARS), total antioxidant status (TAS) and oxidative stress index (OSI) were measured in AF samples. In addition, the *in vitro* antioxidant activity of LF on a cell line was tested.

Results: LF decreased the concentration of TBARS in the AF, with LACTO 4HRS demonstrating the lowest value compared with CONTROLS ($P < 0.0001$). LACTO 4HRS had higher TAS and lower OSI than CONTROLS ($P < 0.0001$ for both). *In vitro*, LF was effective against the oxidative challenge regardless of the time of pretreatment.

Conclusion: In conclusion, LF decreased both *in vivo* and *in vitro* OxS. LF administration may represent an intriguing clinical solution as an adjuvant to treat complications of pregnancy related to inflammation and OxS.

Clinical Study

Vaginal Lactoferrin Modulates PGE_2, MMP-9, MMP-2, and TIMP-1 Amniotic Fluid Concentrations

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Inflammation plays an important role in pregnancy, and cytokine and matrix metalloproteases (MMPs) imbalance has been associated with premature rupture of membranes and increased risk of preterm delivery. Previous studies have demonstrated that lactoferrin (LF), an iron-binding protein with anti-inflammatory properties, is able to decrease amniotic fluid (AF) levels of IL-6. Therefore, we aimed to evaluate the effect of vaginal LF administration on amniotic fluid PGE_2 level and MMP-TIMP system in women undergoing genetic amniocentesis. One hundred and eleven women were randomly divided into controls ($n = 57$) or treated with LF 4 hours before amniocentesis ($n = 54$). Amniotic fluid PGE_2, active MMP-9 and MMP-2, and TIMP-1 and TIMP-2 concentrations were determined by commercially available assays and the values were normalized by AF creatinine concentration. PGE_2, active MMP-9, and its inhibitor TIMP-1 were lower in LF-treated group than in controls ($p < 0.01$, $p < 0.005$, and $p < 0.001$, resp.). Conversely, active MMP-2 ($p < 0.0001$) and MMP-2/TIMP-2 molar ratio ($p < 0.001$) were increased, whilst TIMP-2 was unchanged. Our data suggest that LF administration is able to modulate the inflammatory response following amniocentesis, which may counteract cytokine and prostanoid imbalance that leads to abortion. This trial is registered with Clinical Trial number NCT02695563.

MANAGEMENT: IL RUOLO DEL CONSULTORIO

- LA GESTIONE DELLA MINACCIA D'ABORTO SIA NELLA DIAGNOSI CHE NEL FOLLOWUP E' AMBULATORIALE NELLA STRAGRANDE MAGGIORANZA DEI CASI E NON NECESSITA DI RICOVERO OSPEDALIERO
- LA TERAPIA PUO' ESSERE TRANQUILLAMENTE ESEGUITA AL DOMICILIO
- IL FOLLOW UP PUO' ESSERE FATTO NEI CONSULTORI
- IL CONSULTORIO HA NELLE FIGURE DI OSTETRICA E MEDICO GLI INTERLOCUTORI CORRETTI PER LA GESTIONE DELLA PATOLOGIA
- SI SOTTOLINEA DA PIU' PARTI COME LA MINACCIA D'ABORTO SIA UNA FATTORE DI STRESS PSICOLOGICO NELLA DONNA/COPPIA SOPRATTUTTO QUANDO RICORRENTE: NEL CONSULTORIO TROVEREBBERO ANCHE IL SUPPORTO PSICOLOGICO
- SAREBBE ESSENZIALE RIUSCIRE A RITAGLIARSI I GIUSTI SPAZI PER L'ACCOGLIENZA DELLA PROBLEMATICA «IN URGENZA» SENZA SOVRACCARICARE I PS OSTETRICI PER PATOLOGIE CHE POTREBBERO ESSERE GESTITE IN CONSULTORIO

… GRAZIE DELL'ATTENZIONE