What treatments prevent miscarriage after recurrent pregnancy loss?

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EVIDENCE-BASED ANSWER

Progesterone produces a small but significant decrease in miscarriage among pregnant women with 3 or more unexplained pregnancy losses (strength of recommendation [SOR]: **A**, based on a meta-analysis of 3 small randomized controlled trials [RCTs] with wide confidence intervals). Human chorionic gonadotropin (HCG) reduces the rate of recurrent pregnancy loss among women with 2 or more unexplained pregnancy losses (SOR: **B**, based on a meta-analysis of 4 RCTs with significant methodologic weaknesses).

Four types of immunotherapy are ineffective for preventing miscarriage (SOR: **A**, based on RCTs and systematic reviews of RCTs). Aspirin therapy is ineffective for preventing recurrent miscarriage for women who do not have an autoimmune explanation for previous pregnancy losses (SOR: **A**, based on RCTs).

CLINICAL COMMENTARY

Document your patient's understanding of the risks and benefits

When discussing future childbearing with a woman who has had multiple miscarriages, there are several important issues to address. First, ask what concerns she might have about becoming pregnant again. Second, ascertain how significant another pregnancy loss would be to her. Third, outline the therapeutic options, clearly stating that they alter loss rates but do not guarantee successful delivery. Finally, fully document her understanding of the risks and benefits, including the possibility of treatment failure. Remember, even if the miscarriage rate is reduced from 25% to 20% with treatment, should your patient miscarry, *her* miscarriage rate is 100%!

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Evidence summary

Progesterone. A Cochrane meta-analysis on the use of progesterone to prevent pregnancy loss looked at a subset of 3 small RCTs that evaluated women with 3 or more pregnancy losses. Patients with primary recurrent spontaneous abortion (RSA) (no prior live births), were not differentiated from those with secondary RSA (previous live birth with subsequent miscarriages).

Progesterone administration resulted in a significant reduction in miscarriage compared with placebo (odds ratio [OR]=0.37; 95% confidence interval [CI], 0.17–0.91), independent of administration routes (oral, vaginal, or intramuscular). This benefit was lost in the larger meta-analysis when studies containing women with fewer than 3 pregnancy losses were included.[1]

Human choriogonadotropin. A meta-analysis reviewed 4 trials (n=180 total) of varying methodological quality, which were constructed to determine if women, with at least 2 consecutive miscarriages of unknown cause, derive any protective effect when they receive HCG during the first trimester. Although the overall outcome favored the use of HCG (OR=0.26 compared with placebo; 95% CI, 0.14–0.52), the trials contained major methodological weaknesses (poor description of methods, no power calculations, selection and unclear randomization techniques).[2]

Immunotherapy. A systematic review of 22 RCTs evaluating 4 different types of

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FAST TRACK

Progesterone and HCG may have a small effect in reducing miscarriage; immunotherapy and aspirin are ineffective

immunotherapy for recurrent miscarriage found no significant improvement in live birth rates. All studies were of high quality with a low level of bias. Only one lacked double-blinding.

Immunotherapy types included: paternal leukocyte immunization (PLI) (11 trials, 596 women) (OR=1.05; 95% CI, 0.75–1.47); intravenous immune globulin (IVIG) (OR=0.98; 95% CI, 0.61–1.58); third-party donor cell immunization (3 trials, 156 women) (OR=1.39; 95% CI, 0.68–2.82); and trophoblast membrane infusion (1 trial, 37 women) (OR=0.40; 95% CI, 0.11–1.45).[3]

A subsequent RCT comparing PLI with placebo among 79 women with primary RSA of unknown cause again found no significant difference in live birth rates (89% vs 71%, respectively).[4] However, an additional RCT evaluating PLI (32 patients) vs placebo (19 patients) among women with unexplained primary RSA did find significantly higher birth rates with PLI (84% vs 25%; *P*=.001). This small study used different techniques than previous PLI studies.[5]

A later meta-analysis of 5 RCTs including a total of 246 patients also found that IVIG did not improve the subsequent live birth rate for women with a history of primary or secondary RSA (OR=0.98; 95% CI, 0.45–2.13).[6]

Aspirin. An RCT involving 54 pregnant women (mean age 32.7 years) with a history of primary RSA of unknown cause (negative standard workup) evaluated 50 mg of aspirin daily (n=27) vs placebo (n=27).[7] The method of blinding was not reported.

The live birth rate was identical for the 2 groups (88%). A second (unblinded) trial randomized 805 women from a large referral center (mean age 34 years) with a history of first-trimester RSA (not differentiated between primary and secondary RSA) of unknown cause to either 75 mg of aspirin daily or no treatment.[8] There was no significant difference in the live birth rate between those who took aspirin (251/367; 68.4%) and those who did not (278/438; 63.5%; OR=1.24; 95% CI, 0.93–1.67).

Recommendations from others

The American College of Obstetricians and Gynecologists (ACOG) states that "it has not been shown conclusively that progesterone treatment or corpus luteum support (HCG) influences pregnancy outcome for women with recurrent spontaneous abortion."[9] ACOG does not recommend immunotherapy, citing a lack of demonstrated efficacy (IVIG and PLI), a lack of standards for cell storage and administration, and a risk profile similar to that of blood transfusion (PLI). They recommend "couples with otherwise unexplained recurrent pregnancy loss should be counseled regarding the potential for successful pregnancy without treatment."

REFERENCES

1. Oates-Whitehead RM, Haas DM, Carrier JA. Progestogen for preventing miscarriage. *Cochrane Database Syst Rev* 2003; (4):CD003511.
2. Scott JR, Pattison N. Human chorionic gonadotrophin for recurrent miscarriage. *Cochrane Database Syst Rev* 2000; (2):CD000101.
3. Scott JR. Immunotherapy for recurrent miscarriage. *Cochrane Database Syst Rev* 2003; (1):CD000112.
4. Ramhorst R, Agriello E, Zittermann S, et al. Is the paternal mononuclear cells' immunization a successful treatment for recurrent spontaneous abortion? *Am J Reprod Immunol* 2000; 44:129–135.
5. Pandey MK, Agrawal S. Induction of MLR-Bf and protection of fetal loss: a current double blind randomized trial of paternal lymphocyte immunization for women with recurrent spontaneous abortion. *Int Immunopharmacol* 2004; 4:289–298.
6. Practice Committee of the American Society for Reproductive Medicine. Intravenous immunoglobulin (IVIG) and recurrent spontaneous pregnancy loss. *Fertil Steril* 2004; 82 Suppl 1:S199–S200.
7. Tulppala M, Marttunen M, Soderstrom-Anttila V, et al. Low-dose aspirin in prevention of miscarriage in women with unexplained or autoimmune related recurrent miscarriage: effect on prostacyclin and thromboxane A2 production. *Hum Reprod* 1997; 12:1567–1572.
8. Rai R, Backos M, Baxter N, Chilcott I, Regan L. Recurrent miscarriage-an aspirin a day? *Hum Reprod* 2000; 15:2220–2223.
9. American College of Obstetricians and Gynecologists. ACOG practice bulletin. Management of recurrent pregnancy loss. Number 24, February 2001. (Replaces Technical Bulletin Number 212, September 1995). American College of Obstetricians and Gynecologists. *Int J Gynaecol Obstet* 2002; 78:179–190.