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Role of Progesterone in Recurrent Pregnancy Loss

Recurrent pregnancy loss (RPL) is traditionally defined as three or more miscarriages. Recently ASRM suggested that two or more failed clinical pregnancies may be considered as RPL [1], as etiology of both is similar in contrast to sporadic miscarriages. Approximately 1% of women may suffer from RPL with ≥ 3 miscarriages, but if criteria of two miscarriages is used to define RPL, then nearly 2% of women will be diagnosed as RPL.

RPL may result from large range of etiologies, yet in nearly one third of cases, no cause is identified even after thorough evaluation and such cases are classified as unexplained RPL. Continuation of pregnancy depends on multitude of endocrine events. Various hormones play a critical role in successful growth and development of fetus. Over or under-expression of these hormones may result in failure of pregnancy. These hormones include: Progesterone, Estrogen, Human chorionic gonadotrophin (HCG), Prolactin, Thyroid hormones, Androgens

Progesterone Therapy

Therapeutic value of progesterone in treating RPL and preventing abortion is not well established. There is considerable diversity in opinion regarding progesterone use in abortions. Scientific evidence is not very convincing, but there is tendency to overuse it, as many a times, there is nothing else to offer to these women.

Why Progesterone?

Completion of pregnancy is not possible without

progesterone. Low progesterone levels have been linked to increased risk of first trimester abortion [2]. Removal of corpus luteum may result in failure of pregnancy. Risk of abortion increases as progesterone level decreases.

Progesterone Levels (in ng/mL)	Risk of Abortion ³
>25	3%
20-25	7%
15-20	10%
10-15	30%
5-10	80%
<5	85%

Unfortunately progesterone levels are notoriously unreliable and it is not proved also that exogenous progesterone may help in such cases.

How Progesterone can Support

1. In early pregnancy, it is secreted from ovary by corpus luteum and helps in endometrial growth
2. Progesterone modulates the immune response of mother to prevent rejection of embryo.
 - It produces progesterone induced blocking factor (PIBF) which inhibit NK cell activity.
 - It shifts the balance from unfavourable cytokines Th1 to favourable cytokines Th2.
 - Study conducted by author showed that oral micronized progesterone led to increased rise of Th2 like IL6 ($p=0.001$) and less rise of Th1 like TNF α ($p=0.012$); indicating immunomodulating effect of progesterone [4].
 - Progesterone enhances uterine quiescence and

suppress uterine contractions [5].

- Progesterone may help in prevention of cervical dilatation also.

Issues in progesterone use for RPL: Whether to give?

Which formulation

What route

When to start

How long

Fetal risks

Whether to Give?

Various Cochrane analysis suggested some benefit of progesterone therapy. Initially in 2003, meta-analysis of four trials showed odds ratio (OR) of 0.3 in abortion rate following progesterone therapy [6]. Cochrane 2013 of 14 trials in 2158 cases showed no difference in abortion rate, but sub-analysis on basis of previous history of abortions, miscarriages in the index pregnancy reduced significantly with OR of 0.39 in women with ≥ 3 abortions [7]. An Indian study on 348 cases has shown reduction on abortion rate with dydrogesterone 20 mg daily with abortion rate of 6.9% vs. 16.8% in control group [8]. Recently, the large multicentric trial with vaginal micronized progesterone in 836 women in first trimester did not find the benefit of therapy in RPL. Live birth rate after 24 weeks of gestation was 65.8% in progesterone group vs. 63.8% in placebo (RR 1.04) [9]. It is not known if treatment with intramuscular or oral micronized progesterone would improve the outcome. Our small trial on 90 cases has shown the benefit of oral micronized progesterone in RPL, abortion rate being 3.3% in treatment group vs. 16.7% in non-treated group [4].

Which Formulation and Which Route

There are numerous formulations given by various routes such as intramuscular 17 hydroxyprogesterone, oral dydrogesterone, micronized progesterone. Intramuscular 17 hydroxyprogesterone injections are very painful. Vehicle in it may induce labour and clinical trials have shown increased risk of miscarriage [10]. Vaginal micronized progesterone was found effective in initial retrospective trials, but recent large trial has failed to show its efficacy in preventing abortion [9]. In Cochrane review 2011 on 421 cases of four trials, dydrogesterone was found better with reduction in abortion rate [11]. Indian study has also observed that oral dydrogesterone is effective in reducing abortion rate in RPL, 6.9% vs. 16.85 [8].

Efficacy of intramuscular and oral micronized progesterone is not known yet. Our pilot study on oral micronized progesterone has shown some promising effect, the study is not adequately powered⁴. More trials are needed for oral and injectable micronized progesterone.

When to Start and for how Long

Progesterone treatment has been given for varied duration from 4-24 weeks. In most studies, it is started from diagnosis of pregnancy upto 16-24 weeks of gestation. In our study, we started before 8 weeks of pregnancy and given upto 16 weeks⁷. In patients having history of preterm labour, treatment can be extended till 34 weeks. If LPD is suspected, it can be started in luteal phase.

Fetal and other Risks

There is concern for pregnancy complications like intrahepatic cholestasis of pregnancy, but no increased maternal complications were found in trials^{4,7,8}.

Virilization in fetus is also not reported in humans. Retrospective study on dydrogesterone showed some increased risk of cardiac defects, but it was a very poorly designed study with bias¹². Larger trials with vaginal micronized progesterone found no increase in the risk of congenital malformations among offsprings of cases treated with progesterone⁹. We have large experience of treating these women with micronized progesterone and also their use is common in assisted reproduction, there is no report of increased risk of congenital malformations after therapy.

Opinion for Progesterone in RPL

Meta-analyses of previous trials in 2013 has shown favourable effects specially in cases with previous ≥ 3 abortions. Recent trials with vaginal micronized progesterone has refuted the benefit of treating with this route.

Progesterone is indispensable for creating suitable environment for maintaining pregnancy. Safety of progesterone is well established. Benefit of dydrogesterone is observed. Efficacy of intramuscular or oral micronized progesterone is not known. Because of immunomodulatory effect, earlier initiation of progesterone may improve outcome. There is tendency to overuse this therapy. There is no evidence to support routine use, but in cases with unexplained RPL, it makes no sense to abandon the progesterone supplementation. In author opinion, on

experience basis and as result of pilot study, hope of benefit with oral micronized progesterone seems to be persisting. It is the clinician to decide in judicial manner in selective cases.

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