

## Progesterone for recurrent miscarriage: truth and deceptions

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Recurrent miscarriage is known to affect 0.5–2% of pregnant women, and the standard investigative protocol fails to identify a specific cause in 50% of cases. Progesterone, a key hormone in pregnancy maintenance, has been used to support early pregnancy for decades. A growing body of considerable evidence indicates that in addition to women with luteal phase defects, women with idiopathic recurrent miscarriage may benefit from progestogen treatment, as progesterone has been shown to be an essential immunomodulatory agent in early pregnancy. It plays a critical role in the expression, modulation and inhibition of various growth factors, cytokines, cell adhesion molecules and decidual proteins. Some studies have revealed a remarkable improvement in pregnancy outcome after progestogen supplementation in women suffering from recurrent miscarriage. As most studies on this topic are of insufficient statistical power, further research on the efficacy of progestogen treatment in affected women is required.

**Key words:** recurrent miscarriage; habitual abortion; pregnancy loss; treatment; progesterone; progestogen; immunomodulation.

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### INCIDENCE AND PROGNOSIS

Recurrent miscarriage, defined as the spontaneous loss of three or more consecutive intra-uterine pregnancies with the same partner before 20 weeks' gestation, is known to affect 0.5–2% of pregnant women.<sup>1–3</sup> Repeated pregnancy failures are associated with high emotional distress and financial costs for affected couples and national healthcare systems.

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Studies show remarkable consistency in finding that the risk of miscarriage increases with female age and the number of previous miscarriages.<sup>4–6</sup> A woman who has suffered a single sporadic miscarriage (15–20% of all clinically recognized pregnancies end in a miscarriage, which remains the most common complication of pregnancy<sup>7</sup>) has an 80% chance of her next pregnancy being successful. If having suffered two consecutive miscarriages, the woman has a 70% chance of her next pregnancy being successful. After three consecutive miscarriages, she has a 60% chance of her next pregnancy being successful, although percentages vary depending on the cause of the abortions. Some studies have reported miscarriage risks as high as 55–63% during the first or second trimester in women suffering from recurrent miscarriage.<sup>8–10</sup> Some investigators<sup>11</sup>, but not all<sup>5</sup>, have found the prognosis for a successful pregnancy to be increased by 10–20% in women with at least one previous live birth.<sup>11</sup>

## **PATHOGENESIS AND DIAGNOSTIC WORK-UP**

Recurrent miscarriage is a heterogeneous condition, the pathogenesis of which is multifactorial, complex and poorly understood. In order to provide successful treatment, a thorough understanding of possible reasons for miscarriage and an extensive diagnostic work-up to evaluate associated conditions is required, including hysteroscopy, maternal and paternal karyotyping, spermogram, cervical cultures for chlamydia, ureaplasma and mycoplasma, a comprehensive hormonal status, an evaluation of antiphospholipid syndrome with immunoglobulin (Ig) M and IgG antibody assessment and lupus anticoagulant testing, and testing for other acquired and congenital thrombophilias (i.e. factor V Leiden mutation, protein C deficiency, protein S deficiency, antithrombin III deficiency, prothrombin gene mutation, hyperhomocysteinaemia).<sup>6,12,13</sup> Established aetiological factors, such as anatomical causes (i.e. uterine anomalies and cervical weakness), chromosome abnormalities (e.g. maternal or paternal balanced structural chromosomal rearrangement, usually balanced translocations), coagulation disorders, auto-immune factors, genital infections, endocrine disorders such as hyperprolactinaemia, polycystic ovary syndrome and abnormalities in glucose metabolism (i.e. poorly controlled diabetes), hyperhomocysteinaemia, thyroid abnormalities and antithyroid antibodies, or environmental factors (e.g. heavy smoking, stress) can be found and (apart from chromosome abnormalities and some environmental factors) are usually sufficiently treated, as described in detail by Porter and Scott.<sup>14</sup>

## **PROGESTERONE IN THE TREATMENT OF RECURRENT MISCARRIAGE**

Due to the limitations of our knowledge and understanding of early pregnancy events, the standard investigative protocol fails to identify the aetiology of losses in up to 50% of affected women, and no specific therapy regimens can be offered. In these cases of idiopathic recurrent miscarriage (IRM), several preventive treatment options to avoid further pregnancy failures are discussed.<sup>10,15,16</sup>

Progesterone, secreted primarily by the corpus luteum under the influence of human chorionic gonadotrophin (hCG), plays a paramount role in the maintenance of early pregnancy.<sup>17–19</sup> More than 25 years ago, human studies showed that the removal of the corpus luteum before the eighth week of gestation resulted in a miscarriage.<sup>20</sup> Additionally, luteal phase insufficiency/defect (LPD), defined as serum progesterone levels <10 ng/mL in the mid-luteal phase<sup>21,22</sup>, has been reported to occur in up to

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