Luteal support: Progestogens for pregnancy protection

Salim Daya *

Department of Obstetrics and Gynecology, McMaster University, 1200 Main St West, Hamilton, Ontario L8N 3Z5, Canada

ABSTRACT

Following ovulation, the granulosa cells undergo luteinization and form part of the corpus luteum; this then secretes progesterone that causes secretory transformation of the endometrium so that implantation can occur. The ideal time for implantation is 6–10 days after the luteinizing hormone (LH) surge; implantation occurring outside this optimal window is associated with a higher likelihood of miscarriage. Before the placenta takes over progesterone production, the progesterone produced by the corpus luteum also provides the necessary support to early pregnancy. A defect in corpus luteum function is not only associated with implantation failure but also with miscarriage. In assisted reproduction, both the use of gonadotropin-releasing hormone analogues to prevent the LH surge and aspiration of granulosa cells during the oocyte retrieval may impair the ability of the corpus luteum to produce sufficient progesterone. This may be treated effectively with progestational agents such as progesterone or dydrogesterone, which have a very similar pharmacological profile. Studies indicate that an estrogen may be given during the luteal phase to optimise the estrogen:progestogen ratio to facilitate implantation, although the available evidence is inconsistent in its strength for this hypothesis. In addition to assisted reproduction, progestational agents have shown beneficial effects in the management of patients with recurrent spontaneous miscarriage of unknown cause. In conclusion, despite the wide-spread use and many years of clinical experience, the amount of data from well-controlled clinical trials is currently limited. Further studies are therefore required to establish the optimal treatment situation and type and dose of progestational agent.

© 2009 Published by Elsevier Ireland Ltd.

1. Introduction

Progesterone is essential for the secretory transformation of the endometrium that permits implantation as well as for the maintenance of early pregnancy. Following ovulation, the granulosa cells undergo luteinization and form part of the corpus luteum, which in turn secretes progesterone in response to stimulation by luteinizing hormone (LH) and human chorionic gonadotrophin (hCG). The placenta will subsequently become the main source of progesterone once it has developed sufficiently; this luteo-placental shift generally occurs from around 36 days after the LH surge [1], although progesterone production by the corpus luteum is sustained well into the second trimester of pregnancy [2].

Insufficient progesterone at the time of implantation or during early pregnancy may occur naturally due to luteal phase deficiency, and this can result in infertility and sporadic or recurrent miscarriage. Lack of progesterone may also occur as part of assisted reproduction techniques, including aspiration of the granulosa cells or the use of gonadotropin-releasing hormone (GnRH) agonists or

antagonists. This leads to a range of problems such as diminished in vitro progesterone production by the granulosa cells, delayed endometrial development or abnormal endometrial ultrastructure.

Treatment with progestogens to support embryo implantation and early pregnancy is common in assisted reproduction. The therapeutic use of progestogens not only supports endometrial development, but progestogens like progesterone or dydrogesterone also potentially sustain the survival of the embryo by shifting the immune system towards production of non-inflammatory T-helper (Th)2 cytokines [3,4] and by increasing nitric oxide (NO) production thus improving blood flow and oxygen supply [5,6]. Progesterone also plays an important role in keeping the myometrium quiescent, as demonstrated by enhanced uterine contractility and sensitivity to prostaglandins [7]. This review will consider the basis of uterine receptivity and implantation before looking at clinical evidence for the use of progestational agents in luteal phase support and extending this into early pregnancy and prevention of pregnancy loss.

2. Uterine receptivity and implantation

Progesterone produced by the corpus luteum causes the secretory transformation of the endometrium that is necessary

* Tel.: +1 905 896 7100; fax: +1 905 896 7200.
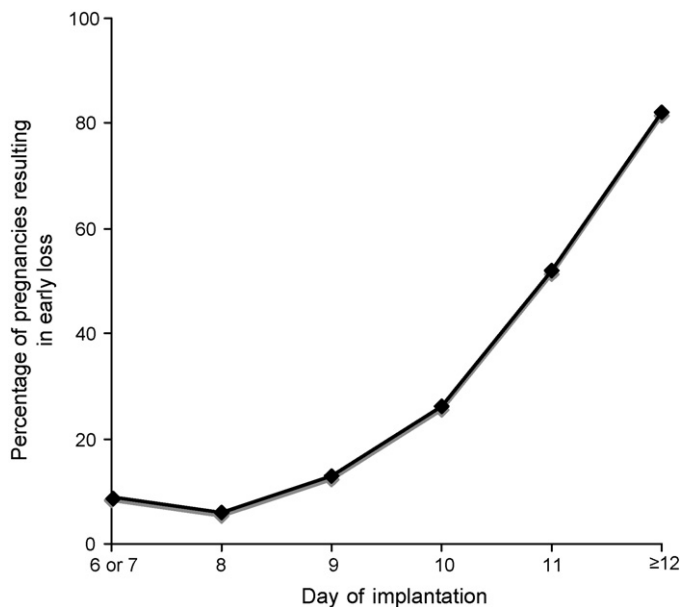E-mail address: dayas@mcmaster.ca.

Fig. 1. Timing of implantation and the risk of early pregnancy loss [9].

for implantation and for the early development of the fertilised ovum. In response to progesterone, the glands become tortuous and secretory and there is an increase in stromal vascularity, thus making the endometrium both morphologically and functionally well prepared for implantation. An impairment of this endometrial receptivity is often seen in women with endometriosis, polycystic ovarian syndrome, unexplained infertility and hydrosalpinges [8].

The endometrium is receptive to implantation for only a few days of the cycle before decidualization; this optimal window of implantation occurs between days 6 and 10 after the LH surge and ovulation. Pregnancies that implant at this time have a lower rate of miscarriage than those that implant later. A study of 189 healthy, naturally occurring pregnancies, of which 141 (75%) lasted for at least 6 weeks after the last menstrual period, found a significant ($p < 0.001$) trend for increasing early pregnancy loss with later implantation [9]. Early loss was least likely when implantation occurred before day 9, but increased to 52% and 82% for implantation on day 11 and after day 11, respectively (Fig. 1). Implantation occurred later (mean: day 10.5) in women with early loss than in those whose pregnancy was maintained at 6 weeks. Of the 141 pregnancies that lasted at least 6 weeks, 118 (84%) had implantation on days 8, 9 or 10.

This window of implantation, which coincides with maximal progesterone production by the corpus luteum, is also a time of maximal pinopode and $\alpha_v\beta_3$ integrin expression in the endometrium (Fig. 2) [10,11]. Pinopodes are small, finger-like protrusions from the endometrial surface that endocytose endometrial fluid, thus increasing the surface of the endometrium and bringing the walls closer to the embryoblast [12]. Integrins, a class of cell adhesion molecules, are heterodimeric glycoproteins that consist of two distinct chains, the α and β subunits. They act as cell surface receptors for extracellular matrix and mediate cell to cell and cell to substrate attachment. The $\alpha_v\beta_3$ integrin is expressed on the apical pole of the luminal surface of human endometrium, where it binds to osteopontin. The secretion of this glycoprotein by the secretory endometrium corresponds both temporally and spatially with the expression of $\alpha_v\beta_3$ integrin [13]. Osteopontin is also recognised by, and bound to, adhesion molecules on the embryo, thus making it an important bridging molecule between the embryo and the maternal epithelium [14]. It has been proposed
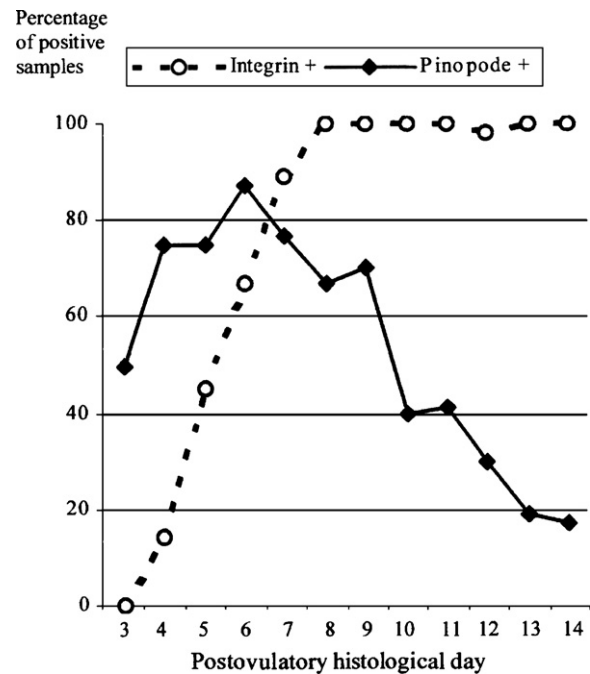

Fig. 2. Temporal expression patterns of endometrial $\alpha_v\beta_3$ integrin and pinopode expression during the luteal phase [11].

that progesterone acts on the endometrium via two different pathways; one direct (endocrine) pathway through which it stimulates gene expression of osteopontin in epithelial cells, and one indirect (paracrine) pathway through which it stimulates growth factor production in stromal cells that, in turn, induces gene expression of $\alpha_v\beta_3$ integrin in epithelial cells [15].

3. Luteal phase dysfunction

As well as its role in implantation, the corpus luteum is an important element in the support of early pregnancy. Because of its unique importance for successful pregnancy, mammals have evolved a complex series of feedback mechanisms that maintain progesterone at appropriate levels throughout gestation. The size of the corpus luteum remains relatively constant for the first 8–9 weeks of pregnancy, followed by a marked regression from week 10 onwards [16]. Removal of the corpus luteum at day 49 (± 2 SEM; $n = 7$) was associated with a fall in progesterone levels and miscarriage while luteectomy at day 61 (± 4 SEM; $n = 5$) resulted in only a transient decrease of progesterone [17]. Similarly, 8 women who were luteectomized a mean of 12.8 (± 1.2 SEM) days after a missed menstrual period experienced a rapid decline in progesterone and subsequent miscarriage [18]. However, if progesterone support was given after removal of the corpus luteum, then the pregnancy progressed normally [19].

A recent study has investigated changes in blood flow in the corpus luteum during the luteal phase and early pregnancy [20]. The relatively high resistance index during the late follicular phase declined with progression towards the luteal phase. By the mid-luteal phase the resistance index was low, thus indicating a high blood flow to the corpus luteum. If the corpus luteum then regressed, there was an increase in resistance index and therefore a reduction in blood flow. The resistance index showed a clear linear correlation with progesterone levels at the mid-luteal phase. Interestingly, in women with luteal phase defect in whom progesterone production was low, the resistance index was significantly higher thus indicating a reduced blood flow. There is therefore a link between adequate progesterone production and