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Article

Luteal phase HCG support for unexplained recurrent pregnancy loss – a low hanging fruit?

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KEY MESSAGE
A single hCG injection in the mid-luteal phase improves outcomes in women with unexplained recurrent pregnancy loss.

A B S T R A C T

Recurrent pregnancy loss (RPL) is defined by two or more failed pregnancies and accounts for only 1–5% of pregnancy failures. Treatment options for unexplained RPL (uRPL) are limited. Previous studies suggest a link between delayed implantation and pregnancy loss. Based on this, a timely signal for rescue of the corpus luteum (CL) using human chorionic gonadotrophin (HCG) could improve outcomes in women with uRPL. This retrospective cohort study included 98 subjects with uRPL: 45 underwent 135 monitored cycles without HCG support; and 53 underwent 142 cycles with a single mid-luteal HCG injection. Based on Log-rank Mantel-Cox survival curves, miscarriage rate and time to pregnancy decreased in the HCG group ($P = 0.0005$). Women receiving luteal HCG support had an increased chance of an ongoing pregnancy compared with those not receiving it (RR = 2.4; 95% CI 1.4–3.6; number need to treat (NNT) = 7; 95% CI 4–18). Subjects receiving HCG support had a significant absolute risk reduction (ARR) of miscarriage ($P < 0.001$; ARR = 11.5%; 95% CI 3.6–19.5; NNT = 9(5–27). These data suggest restoration of synchrony and CL support improves outcomes in women with RPL. Further randomized controlled trials of luteal-phase HCG in women with RPL appears warranted.

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Introduction

While sporadic early pregnancy loss is relatively common, recurrent pregnancy loss (RPL) occurs in only 1–3% of couples (Tang and Quenby, 2010). Current guidelines define RPL as two or more losses (ASRM, 2012; Kutteh, 2015). Known causes for RPL include chromosomal or other genetic abnormalities, endocrine abnormalities such as poorly controlled diabetes, thyroid disease, systemic lupus erythematous (Tien and Tan, 2007), acquired or structural uterine anomalies (Tang and Quenby, 2010), thrombophilia, immunological, infectious and iatrogenic causes (Stephenson et al., 2002, 2007). In approximately 50% of cases of RPL the precise cause remains unknown (Carrington et al., 2005; Duckitt and Qureshi, 2011). While there are directed treatments for known causes of RPL, no consensus for the treatment of the unexplained cases of RPL currently exists (Szekeres-Bartho and Balasch, 2008).

Recurrent pregnancy loss has been attributed to compromised implantation (de los Santos et al., 2003; Dey et al., 2004; Donaghay et al., 2007; Tapia et al., 2008). Georgiana Seegar Jones was the first to suggest that delay in histological development of the endometrium could cause infertility, a concept now termed luteal phase deficiency (LPD) (Jones, 1949). Despite the fact that LPD has fallen out of favour (ASRM, 2012), delayed embryo implantation has been associated with an elevated miscarriage rate. Wilcox and colleagues showed that while most women implant between 6–10 days after ovulation, those achieving pregnancy later than post-ovulatory day 10 were at increased risk of pregnancy failure (Wilcox et al., 1999). The striking correlation between delayed implantation and miscarriage might be attributed to a delay in rescue of the corpus luteum (CL) by embryo-derived human chorionic gonadotrophin (HCG) (ASRM, 2012; Tay and Lenton, 1999; Wilcox et al., 1999), leading to reduced, delayed or curtailed progesterone support. The CL has been shown to play a key role in preparing the endometrium for implantation through its secretion of progesterone, oestradiol, metallopeptidase and inhibins (Savaris et al., 2008). HCG secreted by the embryonic trophoblastic cells appears to both maintain CL function in early pregnancy, while also playing a pivotal role in enhancing implantation and endometrial receptivity (Licht et al., 2007).

The success of an early pregnancy requires synchronous interactions between the endometrium, CL and embryo, while delayed implantation with presumed loss of synchrony, places the pregnancy at risk (Pope, 1988; Wilcox et al., 1999). While supplementation of progesterone alone does not appear to be useful for the treatment of RPL (Coomarasamy et al., 2015; Goldstein et al., 1989; Goldzieher, 1964), systematic reviews suggest benefit from luteal-phase HCG for recurrent loss (Carp, 2010; Morley et al., 2013). Restoring a timely HCG signal during the window of implantation has been shown to improve CL rescue and improve the response of the CL in terms of progesterone output as well (Tay and Lenton, 1999). HCG treatment overcomes luteal phase inadequacy seen in gonadotrophin-stimulated cycles (Peñarrubia et al., 1998). It has also been shown that HCG may have direct effects on the endometrium (Filicori et al., 2005; Fortman et al., 1993; Srisuparp et al., 2001; Stephenson et al., 2002, 2007) and that HCG treatment can postpone apoptotic death of the endometrium (Lovely et al., 2005). Supported by these studies, we chose to investigate our own experience using luteal phase HCG in women with RPL.

While many cases of RPL are clearly explained by anatomic, genetic or immune causes, many others likely represent defects in endometrial receptivity and a delay implantation (Patel et al., 2011). We postulate that HCG activation or support of either the endometrium or CL could benefit those women with recurrent losses and thereby improve outcomes or prevent losses. This study finds evidence to support this hypothesis. Based on the ease and demonstrated safety of HCG administration, we believe that the potential benefit of HCG for the treatment of RPL represents a low hanging fruit in terms of therapeutic options for women with unexplained RPL. To test this, the study compared HCG treatment with control cycles in women with RPL.

Materials and methods

Study design

This retrospective cohort study was approved by the Institutional Review Board at Greenville Health System on 28 March 2016 (Pro00053913).

Setting

Data were analysed from women treated at the Fertility Centre of the Carolinas in Greenville, SC between 1 January 2008 and 31 December 2015.

Participants

Subjects aged between 20 and 40 years of age were included if they had a diagnosis of RPL and if they had received either HCG treatment or no HCG treatment in monitored cycles. RPL for the purposes of this population was defined as 2 or more consecutive first trimester losses. Subjects with RPL cases were chosen from a larger number of patients seen between 2008 and 2016 and had at least one monitored treatment cycle. A standardized work up was used for RPL that included sequential evaluation of endocrine (thyroid stimulating factor, prolactin, testosterone, DHEA-s, day 3 FSH and oestradiol) and structural disorders (hysterosalpingogram and/or sonohysterogram). Immunologic assessment consisted of lupus anticoagulant and anticardiolipin testing; while parental karyotype testing was recommended, it was not performed in all patients due to cost.

Patients were excluded if they had known genetic mutations including balanced translocation or immunological abnormalities such as Sjörgens syndrome, thrombophilia, positive anti-phospholipids, significant uterine anomalies including septate uterus or fibroids, or if they received concomitant progesterone support during the luteal phase. Cycles in which a HCG trigger was administered to induce ovulation were excluded. Subjects were not excluded if they had a history of endometriosis, polycystic ovary syndrome (PCOS) according to the literature (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004) or corrected hypothyroidism.

Variables

The following variables were analysed: age, body mass index (BMI), gravidity, parity, type of fertility medication used (natural cycles, oral [clomiphene citrate and letrozole] and oral with gonadotrophin) and

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