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Improved progesterone levels and pregnancy following *Vitex agnus-castus* (chaste tree) supplementation in a case of recurrent pregnancy loss: A case report

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Abstract

Recurrent pregnancy loss (RPL) occurs in 1% of couples and is defined as three consecutive failed pregnancies. While controversial, evidence exists that adequate levels of progesterone may be an important factor in pregnancy maintenance and that increasing levels of progesterone may increase the likelihood of success. *Vitex agnus-castus* (chaste tree) is a herbal medicine with evidence to support its use in a variety of hormonal conditions, including premenstrual disorder and cyclic mastalgia through modulation of reproductive hormones. This report details a case of RPL in which low progesterone levels were observed. One month of supplementation with Vitex was followed by successful pregnancy with normal levels of serum progesterone and a live birth at full term. A second successful pregnancy followed, also with Vitex supplementation. Although the exact role of Vitex in this case cannot be confirmed, it adds evidence to the hypothesis that this herb may be an effective intervention in cases of RPL, particularly those involving low progesterone, and that more research is warranted.

Keywords: *Vitex agnus-castus*, herbal medicine, progesterone, spontaneous abortion, recurrent pregnancy loss, luteal phase defect.

Introduction

Recurrent pregnancy loss (RPL) has various definitions, making clinical research and diagnosis challenging. For the purposes of this case study, we define recurrent pregnancy loss as at least 3 consecutive failed pregnancies at any time prior to 20 weeks post-menstruation. Pregnancy loss is relatively common and estimated at 15–20% of pregnancies, with the majority occurring prior to 10 weeks[1], while RPL, as defined above, occurs in approximately 1% of couples[2].

Possible causes and contributing factors of RPL include chromosomal abnormalities, thrombophilic disorders such as antiphospholipid syndrome, uterine malformations, infections, hormonal and metabolic dysfunctions such as diabetes mellitus, and sperm DNA fragmentation[1,2]. Low progesterone and luteal phase defect may also play a role[3]. Possible lifestyle factors may include, smoking, obesity and use of alcohol, caffeine or social drugs including cocaine[1]. Other case characteristics associated with RPL may include psychological factors, unmanaged hypothyroidism and diabetes[1]. At least half of RPL cases have no identifiable cause, and it is thought that these cases, as well as most cases of RPL, have multiple contributing factors[1].

Conventional treatment of RPL aims to investigate the cause and initiate appropriate treatment. This may include surgical considerations, anticoagulants or progesterone administration. In couples without an identifiable cause, psychological support pre-conception and in early pregnancy has shown significant benefit[4,5].

Progesterone

Progesterone is a hormone secreted by the corpus luteum post-ovulation and develops the secretory endometrium in preparation for embryo implantation. If implantation occurs, the corpus luteum continues to produce progesterone until weeks 8–10 gestation when the placenta takes over[6]. Progesterone is essential for pregnancy initiation and maintenance. It promotes maternal immune tolerance to the foetus and mitigates uterine contractility[7]. It also triggers the production of progesterone induced blocking factor (PIBF) which possesses anti-abortive effects *in vivo*[7]. Several studies show an association between lower levels of serum progesterone and PIBF and higher risk of spontaneous abortion (SA)[7]. Insufficient progesterone secreted by the corpus luteum may be associated with what is

referred to as a luteal phase defect. Luteal phase defect or deficiency is defined as "insufficient progesterone exposure to maintain a normal secretory endometrium and allow for normal embryo implantation and growth"[8]. Clinically, this may present as a shortened luteal phase and an overall shortened menstrual cycle[9], and primary infertility or recurrent pregnancy loss in first trimester[10]. Assessment of risk for RPL has been based on combined progesterone levels, luteal phase length, and histological features of the endometrium[9]. Luteal phase defect has been controversial due to inconsistencies in the evidence base for diagnosis and treatment. Findings from research have shown that women with RPL are at significant risk for lower progesterone levels in the luteal phase, with 40% of women having luteal phase defect[10,11].

Causes of low progesterone are unclear; however, it has been suggested that latent hyperprolactinaemia (pre-menstrual or stress-induced elevated levels of prolactin) may inhibit corpus luteum development and therefore subsequent progesterone release[12]. Other possible associations include psychological perceived stress[13], excessive exercise[14] and exposure to endocrine-disrupting chemicals[15].

Pharmacological preparations of progesterone such as progestogen have not been shown to benefit pregnancy in the general population; however, a statistically significant decrease in SA in women with RPL has been documented[16]. Additionally, progestogen has been shown to reduce the rate of SA when used in women with threatened miscarriage[17]. While use of exogenous progesterone is common, especially in assisted reproductive technology, concerns exist that intrauterine exposure to exogenous progesterone may increase risk of genital abnormalities in the fetus, such as hypospadias[16].

Vitex agnus-castus

Introduction and biochemistry

Vitex agnus-castus, commonly known as chaste tree, is a deciduous plant with purple-black berries native to Europe and Central Asian countries that is used in botanical medicine[18]. Active constituents of Vitex include flavonoids, diterpenes and glycosides, all of which may exert a hormonal action. *In vitro* studies show dopaminergic activity, resulting in prolactin inhibition. As previously discussed, elevated prolactin in humans may inhibit ovulation, development of the corpus luteum and sufficient progesterone secretion and, therefore, inhibition of excessive prolactin inhibition may subsequently increase progesterone[12]. Additionally, Vitex's action of lowering prolactin levels by way of dopaminergic activity also affects follicle stimulating hormone (FSH), and oestrogen and testosterone in women and men, respectively[19]. Oestrogenic activity is also exerted by linoleic acid found in the fruit of Vitex[19]. Animal studies have shown increased progesterone levels with Vitex supplementation[20].

Uses

Vitex is often used for female reproductive disorders, with the majority of the research focusing on premenstrual syndrome (PMS) and premenstrual dysmorphic disorder (PMDD). Numerous studies have shown significant benefit in PMS and PMDD, despite lack of consistency in preparations of Vitex[19,21-24]. Hyperprolactinaemia may be an important factor in these conditions. As previously discussed, elevated prolactin may inhibit progesterone secretion[12]. Vitex's documented actions of lowering prolactin levels may, in turn, remove its inhibitory effect on progesterone, ultimately normalising progesterone and contributing to positive benefits in PMS and PMDD[19,25]. Additionally, due to prolactin inhibition, Vitex has been shown to improve latent hyperprolactinaemia and cyclic mastalgia[12]. Other research has shown benefits in menopause and fracture healing, and Vitex possessing antimicrobial and antioxidant activity[26].

Positive results on menstrual cycle defects have also been shown for use of *Vitex agnus-castus*. One study involving women with luteal phase defects due to latent hyperprolactinaemia found progesterone levels normalised and luteal phase lengthened after 3 months of supplementation with Vitex[27]. FertilityBlend, a proprietary blend of herbs and vitamins, with Vitex as a key component, found a significant increase in luteal progesterone levels as well as pregnancy rates in a group taking the supplement for three months[28]. However, due to the proprietary blend of multiple ingredients, outcomes cannot be attributed to Vitex alone. While Vitex has well-documented hormonal activity, which may theoretically influence fertility, we have found no research directly testing the use of *Vitex agnus-castus* for low progesterone in RPL, with primary outcome of maintained pregnancy to second trimester.

Case presentation

Presenting concern

AB, a Caucasian woman presented at age 29 with concerns of recurrent pregnancy loss (RPL). She reported a history of four chemical pregnancies detected by urine or serum bHCG, three of which were in the preceding eight months. These pregnancies resulted in complete spontaneous abortion (SA) at five weeks' gestation without intervention.

Laboratory assessment was completed immediately prior to and during the fourth SA. At 5 weeks plus 2 days' gestation, bHCG was 459 IU/ml (normal range: 18–7340 IU/ml) and progesterone was 22.1 nm/L (1st trimester normal range: 18–150 nm/L). At 5 weeks plus 4 days, bHCG was 374 IU/ml and SA occurred two days later.

Past medical history

AB reported a history of moderate facial acne vulgaris and moderate primary dysmenorrhea since menarche. Bilateral dermoid ovarian cysts approximately 1 cm by 2 cm in size were an incidental finding on ultrasound

four years prior. They were monitored annually by ultrasound with no significant change. She had no history of abnormal Papanicolaou tests. AB reported no family history of infertility or genetic conditions. The patient's partner reported no past or current medical concerns and no family history of infertility or genetic conditions.

Psychosocial history

The patient lives with her husband and reports moderate work stress, which she manages with mindfulness meditation.

Medication

AB was not taking any prescription or over-the-counter medication. She used topical benzole peroxide for management of acne vulgaris. She was supplementing folic acid (methylfolate 1000 mcg per day).

Diagnostic focus and assessment

Other laboratory assessment included TSH 0.87 mIU/L (0.3–5.0 mIU/L). Physical examination was within normal limits.

Therapeutic approach

A prescription was made for *Vitex agnus-castus* herbal supplement at a dose of 166.6 mg of 6:1 fruit extract from 1000 mg of fruit per day (Brand: Mediherb, 2 capsules per day). AB reported a high level of compliance and no adverse reactions.

Follow-up and outcomes

After one month of supplementation, the patient completed a home pregnancy test, which was positive. Laboratory assessment completed at 5 weeks plus 2 days' gestation revealed bHCG of 1200 IU/ml and progesterone of 85 nm/L (Table 1). Ultrasound examination two days later revealed a singleton uterine pregnancy.

This laboratory and imaging assessment took place with an obstetrician/gynaecologist, who completed a fellowship in reproductive endocrinology and infertility, and to whom AB was referred by her primary health care provider. The positive home pregnancy test preceded the initial visit with this clinician and, thus, no other investigations related to causes of infertility were completed. The specialist advised the patient to discontinue the herbal supplement at 5 weeks plus 4 days and prescribed vaginal pessaries of progesterone (200mg twice per day) until 10 weeks' gestation.

Subsequent ultrasounds and screening testing were normal and the patient had a healthy pregnancy, resulting in spontaneous vaginal delivery of a healthy infant at full term.

When the patient was 15 months' postpartum, she restarted the Vitex formula. One month later she conceived naturally. The Vitex formula was continued until 8 weeks' gestation and then discontinued. Discontinuation at 8 weeks was based on the placenta assuming the role of progesterone production from the corpus luteum at this point in pregnancy and the patient's desire to discontinue intervention at the earliest opportunity. At the time of writing, the patient is 38 weeks' pregnant. Ultrasound assessment at 12, 20 and 28 weeks gestation revealed a healthy, singleton, uterine pregnancy.

Discussion

The precise role that supplementation with Vitex played in this case is unclear; however, repeated blood work and a proposed biological mechanism lend support to the hypothesis that the intervention may raise progesterone levels or normalise another physiologic parameter, resulting in maintenance of the pregnancy.

Proposed mechanism

In this case, progesterone levels improved between subsequent pregnancies following Vitex supplementation, and pregnancy was subsequently maintained. Adequate progesterone production by the corpus luteum is known to play an important role in the maintenance of pregnancy through the first eight weeks of gestation through a variety of mechanisms. As discussed, Vitex may increase progesterone levels by way of inhibiting prolactin. Prolactin levels were not measured in this case; therefore the role of prolactin is unclear. Documented uses of Vitex supports the proposed mechanism of action of increasing progesterone levels leading to maintained pregnancy.

Strengths and limitations

A strength of this case report is that the laboratory testing was completed at the same gestational age for two consecutive pregnancies, allowing for comparison prior to and after Vitex supplementation.

This report has limitations. Progesterone levels were not assessed in the earlier pregnancies, so it is unclear if low progesterone was associated with previous SAs. Although it may be suspected, this cannot be confirmed. Unfortunately, prolactin levels were not assessed in this case, which also limits the ability to draw inferences about the therapeutic mechanisms.

Table 1: Laboratory values for AB at 5 weeks plus 2 days gestation

	Reference range	4th pregnancy with no intervention	5th pregnancy with Vitex supplementation
bHCG	18–7340 IU/ml	459 IU/ml	1200 IU/ml
Progesterone	18–150 nm/L	22.1 nm/L	85.0 nm/L
Outcome		Spontaneous abortion at 5 weeks +6 days	Pregnancy maintained with full-term live birth

Safety

The safety profile of Vitex is well established and adverse events have been shown to be infrequent, mild and reversible. Despite acknowledgement that Vitex may have a therapeutic role[29], use in pregnancy and lactation is currently not recommended based on lack of safety evidence[30].

Further research

Few therapeutic options are available for women experiencing RPL in the absence of an identifiable cause. While therapeutic progesterone is a valuable tool, some concerns about side effects to the developing foetus have been cited or hypothesised[16]. The potential for Vitex to play a role in the maintenance of hormonal balance in early pregnancy and prevention of SA would be a valuable therapeutic tool. This case report highlights a need for further research on this topic in order to elucidate the effect of Vitex on hormonal balance, progesterone and prolactin in particular, and the role that the herb may play as an intervention in cases of RPL. Randomised controlled trials investigating Vitex supplementation in women with RPL are needed to further explain its clinical effectiveness for progesterone augmentation, prevention of SA and safety in pregnancy.

Conclusion

This report details a case of two successful pregnancies following RPL with *Vitex agnus-castus* supplementation. Vitex may be useful in the prevention of recurrent SA related to sub-optimal progesterone. More research, including intervention studies, is needed to fully investigate the potential for efficacy and safety.

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Permission

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Conflict of interest

The authors declare no conflicts of interest.

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