Clinical importance of vascular LH/hCG receptors – a review

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SUMMARY

It was believed for a long time that functional LH/hCG receptors were present only in gonads. Recent studies have demonstrated, however, that these receptors are also present in several nongonadal organs in the human body. Uterus is one of them. Besides two uterine layers, endothelial cells and smooth muscle of blood vessels in the uterus also contain these receptors. In vivo administration of hCG decreased vascular resistance in the human uterus and in vitro treatment increased vasodilatory and decreased vasoconstrictive eicosanoids in the vessels. These findings led us to investigate whether hCG administration to patients with signs of threatened abortion has any beneficial effect. Patients were treated with either magnesium or progesterone and/or hCG. The results showed that the frequency of patients reaching second trimester was higher when hCG was used, which was paralleled by a significant decrease in uterine vascular resistance. Patients who reached term after treatment had decreased incidence of preterm delivery and intrauterine growth retardation. In conclusion, we suggest that uterine vascular LH/hCG receptors play an important role in the peri-implantation period by increasing uterine blood flow through vasodilatation and also perhaps through angiogenesis and trophoblast invasion, resulting in therapeutic benefit. Reproductive Biology 2001 1 (2): 5-11

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INTRODUCTION

For many years, our knowledge about the localization and function of LH/hCG receptors was constrained to only the gonadal tissues. Neither their localization nor function in extragonadal tissues of human body was suspected until perhaps 15 years ago. The first reports [10, 13, 19, 34] on extragonadal LH/hCG receptors initiated further studies to characterize them in detail. The LH/hCG receptor mRNA and protein were found and characterized in the human myometrium [23], placenta [10], fallopian tube [13], leukocytes [16], breast [17, 22], brain [12] as well as many other tissues. Subsequent studies revealed the presence of these receptors in not only tumor tissue but also found association between receptor density and oncologic process [11]. The association between structural change in the receptor and the defective regulation was found in choriocarcinoma cells [14].

The presence of extragonadal LH/hCG receptors raised the possibility of their functions and many subsequent studies were directed to address this possibility [13, 18, 26, 27, 28, 29, 30].

LH/hCG RECEPTORS OF THE UTERINE ARTERIES

The findings on LH/hCG receptors in human uterine arteries [23] led to detailed characterization [20, 28]. Endothelial cells contain more receptors than the vascular smooth muscle and both cell types in vessels of smaller diameter contain more LH/hCG receptors than larger vessels. Both size arteries contain multiple receptor mRNA transcripts and an 80 kDa receptor protein [28]. Other studies found that uterine blood vessels of numerous species also contain functional LH/CGR receptors [2, 7, 24, 36, 37].

The higher receptor levels in smaller uterine arteries that determine blood flow resistance suggest that LH and hCG play a role in regulating local blood flow. It was hypothesized that the receptor activation increases uterine blood flow by vascular smooth muscle relaxation. A potential candidate for signaling was the local eicosanoid biosynthetic pathway. It was based on previous findings in different tissues where the LH/hCG receptors were found to be coupled to increasing eicosanoid biosynthesis [9, 25, 27].

To test this possibility, uterine blood vessels were treated with highly purified hCG (CR 127 NIH) in short term tissue culture conditions [20, 28]. The treatment resulted in a dose- and time- dependent significant change in immunoreactive eicosanoid synthases and eicosanoid formation in the vessel walls favoring the increase in vasodilatory eicosanoids. Next, nonpregnant patients in an infertility program were treated with 10,000 IU hCG i.m. and the uterine vascular resistance was measured by a pulsed Doppler ultrasound probe
before and 16 hrs after hCG administration. The results showed a decrease in the resistance index without any significant change in serum estradiol and progesterone levels. Thus, the effect appears to be due to direct vasodilatory action of hCG. In vitro studies with isolated uterine artery segments showed a direct hCG effect on vascular smooth muscle tone [7]. The blood flow regulatory effect of LH/hCG receptor activation was also shown in other species such as rat [8], pig [37] and cow [24].

All these findings led to investigating whether hCG administration affects uterine blood flow in early pregnant patients and, if so, whether it could influence the course of pregnancy in women with threatened and/or repeated abortions.

**EFFECT OF hCG ADMINISTRATION IN EARLY PREGNANCY**

A vast majority of pregnancy losses occurs in the first trimester [4, 33] and implantation failure is the most common cause. Despite extensive research, very little is known about the etiology of pregnancy failure and how to prevent it. A successful implantation requires increased blood flow and optimal invasion of trophoblasts into the spiral arteries. The implantation failure may result in threatened abortion, spontaneous abortion, recurrent miscarriages and sequelae, such as intrauterine fetal growth retardation, preeclampsia, and/or premature labor in those pregnancies that survive through term.

Until recently, threatened abortion patients were treated with magnesium. Regarding previous data, it was assumed that the administration of hCG with or without progesterone might increase the uterine blood flow in early pregnancy and improve clinical outcome in patients with signs of threatened abortion. To test this hypothesis, patients were treated with hCG, progesterone or magnesium or their combination. The primary goal was to determine the differences between treatment groups in reaching the second trimester with a viable fetus. Inclusion of hCG in the treatment protocols resulted in a significant decrease in the spontaneous abortion rate [31]. Treatment with hCG alone yielded almost the same results as when it was combined with progesterone [31]. Moreover, hCG treatment was found to be more effective than treatment with progesterone [31]. While the hCG addition to the magnesium therapy decreased the abortion rate by 46.8%, the progesterone addition decreased it by only 18.4% [31].

Uterine blood flow before and 16 hrs after hCG administration was measured with pulsed Doppler vaginal ultrasound probe [31] similar to a previous study [28]. It was found that, after hCG administration, the blood flow resistance decreased significantly without a noticeable change in serum estradiol and progesterone levels.
In the next study\(^2\), patients with signs of threatened abortion were treated with micronized progesterone plus hCG versus magnesium alone. Uterine Doppler blood flow and serum hormone levels were measured at the beginning of therapy and then every two weeks. The data showed that uterine vascular resistance was significantly lower in the hCG and hCG/micronized progesterone-treated groups compared with the magnesium-treated group. Estradiol, progesterone and prolactin levels increased more in the hCG/micronized progesterone-treatment group than in the magnesium-treatment group until the end of the first trimester. Therefore, a long-term beneficial effect of hCG treatment may also include an increase in uterine blood flow through mediation by steroid hormones [3].

This raised the question of whether hCG treatment can improve the long-term clinical outcome. Delivery data of patients treated either with hCG or magnesium in early pregnancy were analyzed. Although the number of patients in this ongoing study is still low, a clear decrease in intrauterine growth retardation and preterm deliveries was seen after hCG treatment compared to that of the magnesium treatment [31].

CONCLUSIONS

The vascular LH/hCG receptors were discovered and characterized in the last decade and understanding their functional significance is still in progress [7, 20, 21, 24, 28, 31, 32, 36, 37]. The knowledge about their localization in the uterine vascular system led to functional characterization. These studies revealed that direct hCG actions on blood vessels without involving ovarian steroid hormones cause a short-term increase in blood flow. The long-term increase, however, may involve steroid hormone response to hCG treatment. It is possible that the steroids work by increasing the density of the LH/hCG receptors [35], thus further sensitizing the vessels to circulating LH and hCG [5, 6, 35].

The question can be raised whether therapeutic hCG administration stimulates lutein cyst formation in early pregnancy. According to our experience, hCG administration did not cause lutein cyst formation in any of the patients treated during early pregnancy even if they became pregnant after ovulation induction.

\(^2\) Toth P Gimes G Valent S Paulin F 2001 Micronized progesterone and hCG treatment decrease uterine vascular resistance and improves pregnancy outcome. Journal of the Society for Gynecological Investigation 8 (Supplement) 289A.
The long-term beneficial effect of hCG treatment may involve uterine vascular relaxation, increased trophoblast invasion [38], angiogenesis [1], etc. While our understanding of the regulation of uterine vascular functions and implantation [15] by hCG is increasing, very little is known about the regulatory role of hCG in fetal (umbilical) vessels.

In conclusion, hCG treatment during early pregnancy for threatened and repeated abortion is safe and effective, and short- and long-term benefits are related, in part, to vasodilatory effects.

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REFERENCES


