Perspectives

Corpus Luteal Contribution to Maternal Pregnancy Physiology and Outcomes in Assisted Reproductive Technologies

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Author Contributions: KPC conceived and developed the hypothesis; VLB contributed to the development of the hypothesis

Running Head: Role of the Corpus Luteum in Maternal Adaptations to Pregnancy

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Abstract

Investigations in the rat model of pregnancy indicate an important role for the corpus luteal (CL) hormone relaxin in the maternal circulatory and osmoregulatory changes in pregnancy, which are epitomized by profound vasodilation and modest hypoosmolality, respectively. In a pilot study of infertile women who became pregnant through donor eggs, in vitro fertilization and embryo transfer, the gestational rise in glomerular filtration and fall in plasma osmolality were markedly subdued. Because these women were infertile, they lacked a CL and circulating relaxin (and possibly other vasoactive CL hormones). Based on these findings in pregnant rats and women, we hypothesize that infertile women conceiving through donor eggs will have overall subdued circulatory changes (e.g., attenuated reduction in systemic vascular resistance and subdued increase in cardiac output) particularly during early pregnancy when CL hormones predominate before the full development and maturation of the placenta. In contrast, infertile women conceiving by autologous eggs retrieved after ovarian stimulation and fresh embryo transfer may have a relatively hyperdynamic circulation due to the presence of many CL (up to 20 or more) and higher circulating levels of vasodilatory ovarian hormones such as relaxin. Emerging evidence suggests that women undergoing Assisted Reproductive Technologies (ART) have increased risk for adverse pregnancy outcomes such as preeclampsia and small for gestational age babies. This increased risk may be partly caused by the maternal milieu, which is not physiological in ART pregnancies due to the abnormal status of the CL.

Keywords: cardiovascular, renal, preeclampsia, intrauterine growth restriction, relaxin, in vitro fertilization
Assisted reproductive technology (ART) began in 1978 with the birth of Louise Brown (32). Since 1978, there have been 3-4 million live births conceived by ART worldwide and the use of ART has doubled over the past decade (32). In 2010, there were 154,417 ART cycles performed yielding over 47,000 live births in the US (32). In pregnancies achieved through ART, the number of corpora lutea (CL) vary, while during a natural pregnancy, there is typically one CL. In general, there are two types of ART pregnancies: those achieved by using either autologous or donor eggs. Briefly, in the case of autologous eggs, after in vitro fertilization (IVF) and fresh embryo transfer (ET), there are multiple corpora lutea (CL) secondary to the ovarian stimulation used to enhance follicle numbers. Frozen embryos can be transferred either during a natural or medicated cycle. During a natural cycle, there is typically one CL, while in a medicated cycle involving pituitary suppression, there is no CL. Donor-egg recipients may have ovarian failure or be medicated, and therefore, in either case do not have a CL. To summarize, ART can occur in the setting of nil, one or multiple CL. Because the CL serves as a major source of reproductive hormones during early pregnancy before establishment of the placenta, we hypothesize that the altered CL status of ART conceptions could impact maternal physiology and pregnancy outcomes.

Indeed, emerging epidemiological evidence suggests that pregnancies conceived by ART may be at increased risk for abnormal pregnancy outcomes including pregnancy induced hypertension and compromised fetal growth (9, 11, 14, 17, 23, 27, 31). Furthermore, women and their children who suffer from these obstetrical complications may be at higher risk for future adverse cardiovascular events (8, 21, 25). Of perhaps even greater concern is that many of the women who conceive by ART are typically of advanced maternal age, which alone may compromise cardiovascular adaptation during pregnancy. Potential explanations for adverse obstetrical outcomes following ART are (i) multiple gestations, although increased risk is
observed with singleton pregnancies, (ii) increased maternal age, although increased risk is observed after matching for maternal age, (iii) underlying infertility, (iv) increased immunological challenge in the case of donor gametes, and (v) iatrogenic reasons related to embryo culture conditions. However, another possible explanation is that other naturally occurring or iatrogenic causes may contribute to adverse pregnancy outcomes, i.e., absence of a CL in donor-egg recipients or excessive number of CL after ovarian stimulation in women receiving autologous eggs.

More specifically, we hypothesize that women conceiving by ART manifest abnormal cardiovascular, renal and plasma volume regulation particularly during early pregnancy that, in turn, predispose to pathological outcomes such as preeclampsia (PE). That is, ART pregnancies begin in a maternal milieu, which is not physiological due to the abnormal status of the CL and its production of hormones including relaxin and sex steroids. Although relaxin is a likely candidate for vasodilatory and angiogenic effects, other CL products besides relaxin may circulate and have similar actions. Absent or excessive circulating levels of these CL factors in the case of donor-egg recipients and ovarian stimulation, respectively, may perturb maternal circulatory adaptations (and decidualization) in pregnancy, thereby precluding optimal placental development and fetal growth. In pregnancies conceived by ART, there is a CL “dose response,” the number of CL ranging from 0 to >20, with CL products such as relaxin being either undetectable or supraphysiological in the blood (24). (Note that progesterone is administered for luteal support in ART cycles including those with absent CLs.) We propose that the absence or excess of CL and CL hormones will result in a relatively “hypodynamic” or “hyperdynamic” maternal circulation, respectively, during early gestation (Fig. 1). As part of an endocrinologic continuum beginning in the luteal phase, CL hormones are likely to be major regulators of maternal adaptations in early pregnancy. Thus, the concept of the luteal-placental shift pertains not only to the organ source of circulating sex steroids, but should be expanded to
include maternal cardiovascular, renal and plasma volume regulation, of which the development
and maintenance phases will be mainly dictated by hormones derived from the CL and
placenta, respectively, but with overlap during mid-gestation (Fig. 2).

Optimal maternal cardiovascular, renal and volume adaptations in early pregnancy are critical to
successful pregnancy outcomes (1, 5, 7, 22, 30). Deficits or excesses in these maternal
pregnancy adaptations in ART patients are likely to ultimately impinge upon uterine blood flow,
and consequently fetal and placental growth. During the clinical phase of PE, a picture opposite
to normal pregnancy is observed, i.e., hypertension secondary to profound vasoconstriction of
maternal organs such as the kidneys. Despite a reciprocal decrease in cardiac output
consequent to raised ventricular afterload, arterial pressure is still markedly elevated in PE.
Thus, a low cardiac output-high arterial resistance state prevails, and plasma volume is
contracted during clinical disease (a relatively “hypodynamic” circulation for pregnancy).
Interestingly, recent evidence suggests that a low cardiac output-high arterial resistance state
during the first trimester precedes the clinical onset of normotensive intrauterine growth
restriction (IUGR) or severe early onset PE with IUGR (5, 22, 30). Thus, failure or deficiency of
maternal vasodilation in early pregnancy is associated with these adverse obstetrical and
perinatal outcomes, and may predispose or contribute to them. In contrast, the prodromal period
of late onset PE and/or gestational hypertension is characterized by an excessively high cardiac
output-low arterial resistance state during the first trimester (a “hyperdynamic circulation”),
which then “crosses over” to a vasoconstrictive pattern during the clinical phase (2, 5, 7). Taken
together, abnormal maternal circulatory dynamics characterized either by a “hypodynamic” or
“hyperdynamic” circulation predates clinical symptoms of major obstetrical disorders, and as
such, may play a causal or predisposing role. Insofar as pregnancies achieved by ART may
manifest similarly perturbed maternal circulatory dynamics (vide supra), they may be likewise
prone to obstetrical pathologies.
Supporting Evidence for an Important Role of the Corpus Luteum in Maternal Adaptations to Pregnancy

**Administration of Relaxin, a Corpus Luteum Hormone, Mimics Maternal Vasodilation of Pregnancy**

Gravid rats and women undergo similar maternal circulatory adaptations to pregnancy typified by massive vasodilation, which is mimicked by relaxin administration to non-pregnant rats and women [reviewed in (4)]. In addition, many maternal adaptations to pregnancy are anticipated in the luteal phase of the menstrual cycle, albeit of lesser magnitude [(3) and reviewed in (12)]. The pattern of change in circulating relaxin (20, 28) corresponds with the circulatory and osmoregulatory changes in the luteal phase and early pregnancy suggesting the contribution of relaxin to these maternal adaptations.

**Relaxin Neutralization/Elimination from the Circulation Inhibits Maternal Vasodilation**

Not only does relaxin administration to non-pregnant rats mimic maternal circulatory and osmoregulatory responses to pregnancy (vide supra), but immunoneutralization/elimination of relaxin inhibits maternal vasodilation, increases in global arterial compliance (AC) and osmoregulatory changes in midterm pregnant rats [(6, 19), and reviewed in (4)]. Interestingly, in late pregnant rats, relaxin immunoneutralization only partly inhibits maternal systemic vasodilation and increases in global AC (KP Conrad et al., unpublished), suggesting a vasodilatory role for placental-derived hormone(s) such as PlGF [(18), and citations therein].

**Absence of the Corpus Luteum in Women Impairs Renal Function Changes during Pregnancy**

In women conceiving by egg donation, IVF and ET, we observed a markedly subdued gestational increase in GFR [and blunted decline in plasma osmolality] during the first trimester;
later time points were not studied (26). One explanation is that these women lack a CL and circulating CL factors like relaxin. Do these deficiencies represent just the “tip of the iceberg”? In fact we do not know, because to our knowledge, there are no reports of other maternal cardiovascular adaptations such as systemic vascular resistance, cardiac output and global AC in ART pregnancies. Since the women who received donor eggs lack a CL, CL factors such as relaxin are implicated in mediating these physiological adaptations in the 1st trimester; however, unlike the animal studies in which specific neutralizing antibodies were employed, it was not possible to prove a specific intermediary role for relaxin in this study (26). In fact, residual changes were observed despite the lack of circulating relaxin suggesting the contribution of other hormones during early pregnancy in women, e.g., hCG (10), estrogen and progesterone, or their metabolites. While estrogen has little or no effect on plasma osmolality (15) nor on the renal circulation, progesterone may exert modest renal vasodilation (reviewed in ref. (12)). Estrogen may contribute to the vasodilation of other maternal circulations during early pregnancy (16), if systemic vasodilation is discovered to be partly, but not completely attenuated in donor-egg recipients.

**Low 1st Trimester Serum Relaxin Predisposes to Preeclampsia**

Although serum relaxin levels may not be different during disease (29), spontaneously conceiving women with serum relaxin in the lowest quartile (< 500 pg/ml) during the first trimester have an adjusted odds ratio of 7.5 for developing PE (P<0.02) (13).

**In summary**, we advance the concept that maternal cardiovascular, renal, osmoregulatory and volume adaptations are abnormal during pregnancy in many women conceiving by ART. That is, in women conceiving by ART, pregnancy begins in a state that is not physiological for the mother secondary to abnormal CL status with CL numbers ranging from 0 to >20. In turn, this may be a contributing factor to the increased incidence of obstetrical complications after ART.
Clinical Implications for Oocyte Donation and IVF with Autologous Oocytes

In the case of egg donation, IVF and ET, in which circulating relaxin and other CL factors are absent, relaxin or a small molecule mimetic might be included in the hormonal regimen administered for luteal support. In the case of ovarian stimulation, IVF and ET, less ovarian stimulation might be recommended, in order to reduce the number of CL, and thus, circulating vasodilatory factors like relaxin, which emanate from the CL. The ultimate goal would be to determine whether these potentially corrective strategies would restore normal maternal cardiovascular and volume regulation in ART pregnancies, thereby preventing or reducing the risk of pathological pregnancy outcomes.
Acknowledgements

Supported by National Institutes of Health Grants PO1 HD065647, RO1 DK063321 and RO1 HL067937. KPC gratefully acknowledges the productive collaborations with Lee A. Danielson, John M. Davison, Arun Jeyabalan, Jacqueline Novak, Laura J. Parry, Mark S. Segal and Sanjeev G. Shroff.
Figure Legends

**Figure 1.** Hypothetical impact of Assisted Reproductive Technologies (ART) on maternal circulatory changes in pregnancy. Both mother and offspring who suffer obstetrical complications such as preeclampsia and fetal growth restriction are predisposed to future cardiovascular disease (see Text).

**Figure 2.** The concept of the luteal-placental shift applied to maternal blood flow in pregnancy (e.g., cardiac output, and renal blood flow among other organ circulations). The vertical dotted line demarcates the end of the 1st trimester.
References


ART

Ovarian Stimulation: Multiple Corpora Lutea

Hyperdynamic Circulation

Abnormal Maternal Circulatory Adaptations to Pregnancy

Predisposition to Abnormal Obstetrical Outcomes

Predisposition to Later Cardiovascular Disease

Egg Donor Recipient: Absent Corpus Luteum

Hypodynamic Circulation

Figure 1
Figure 2

Maternal Blood Flow

PLACENTAL HORMONES

CORPUS LUTEAL HORMONES

DEVELOPMENTAL PHASE

MAINTENANCE PHASE

Weeks of Gestation