Corpus luteum across the first trimester: size and laterality as observed by ultrasound

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Objective: To study the site and size of the corpus luteum (CL) across the first trimester of pregnancy.
Design: Retrospective observational study of 1,806 ultrasound scans performed at 5 to 9 (+6 d) weeks' gestation, as well as a prospective study (n = 313) performed at 10 to 13 (+6 d) weeks' gestation.
Setting: Four ultrasound practices across Victoria, Australia.
Patient(s): Two thousand one hundred nineteen pregnant women.
Intervention(s): Transvaginal ultrasound.
Main Outcome Measure(s): Side and size (diameter) of the CL.
Result(s): At 5 to 9 weeks' gestation, the mean CL diameter was 19.3 mm, with no statistically significant variation across each gestational week. Corpus luteum size then statistically significantly declined at 10 to 13 weeks' gestation, with a mean diameter of 16.85 mm. Of 237 women in whom both ovaries were visualized at 10 to 13 weeks' gestation, a CL was seen in 82% of cases. A statistically significant right-sided bias was observed in both groups (54% at 5–9 wk gestation, 56% at 10–13 wk).
Conclusion(s): The CL remains static in size across 5 to 9 weeks' gestation, then its size declines or it disappears from 10 to 13 weeks. A novel right-sided ovulation bias occurs in human beings. (Fertil Steril® 2008;90:1844–7. ©2008 by American Society for Reproductive Medicine.)

Key Words: Corpus luteum, laterality of ovulation, size, ultrasound

The corpus luteum (CL) is a vital endocrine organ. Historical lutectomy and oophorectomy experiments on women seeking termination of pregnancies have shown that its removal before the 7th week always results in miscarriage (1). Its relative size, as assessed by ultrasound, may be a surrogate marker of endocrine activity because it correlates with serum P levels in human beings (2) as well as in animals (3, 4). Our centers routinely document the presence and diameter of the CL of all early pregnancy ultrasound scans. We set out to document the changes in CL diameter across the first trimester of pregnancy, as measured by ultrasound, in a large cohort of pregnant women.

Because the CL forms at the site of the collapsed dominant follicle, the ovary in which it is seen indicates the side on which ovulation occurred. Ultrasound studies examining the laterality of ovulation all have used the dominant follicle as a surrogate marker of ovulation (5–7). Whereas initial studies found that ovulation occurred with equal frequency on both sides (5, 6), two larger studies suggested a novel right-sided bias. Among 2,090 observations, Fukuda et al. (8) reported that the dominant follicle was found to be the right one in 55% of cases, and Jarvela et al. (7) concluded that 57% of 477 women in their cohort ovulated on the right. Although the dominant follicle is likely to be an accurate reflection of ovulation, it is a preovulatory structure. Furthermore, there are instances in which more then one large follicle is seen by ultrasound, making it difficult to determine which one is the true dominant follicle that will ovulate. Thus, the CL represents a more definitive marker, indicating on which side ovulation occurred. We used the CL to examine the side of ovulation in our cohort to see whether we could confirm this right-sided bias.

Given that it has been shown elsewhere that a CL appears detectable in 95%–98% of cases at 5 to 9 weeks (9, 10) we collected data on laterality and size retrospectively for these gestations. In contrast, the ability of ultrasound to detect the presence of a CL at 10 to 13 weeks' gestation never has been reported. Although the CL still may be readily detected, it also could have started to involute at this gestation, or its vascularity may have diminished sufficiently to render it too difficult to see on ultrasound. Therefore, we collected data at these gestations prospectively to also determine how often the CL actually is detectable by ultrasound.

MATERIALS AND METHODS

We performed an observational study, collecting data on laterality and CL diameters from women having early pregnancy ultrasounds in cases in which there was no concern regarding viability. For all scans from 6 weeks (+2 d) onward, we only included those that had demonstrable cardiac activity without

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bradycardia. Ethics approval was obtained for this study from the Epworth Hospital Human Research and Ethics Committee (Richmond, Victoria, Australia).

For reasons outlined in this article's introduction, we performed two studies, one on a large retrospective cohort of 1,806 women who attended an ultrasound appointment at 5 (+0 d) to 9 (+6 d) weeks' gestation and a prospective study on 313 women who presented at 10 (+0 d) to 13 (+6 d) weeks' gestation.

Data for the retrospective study were collected from ultrasound reports that were generated from four obstetrics and gynecology ultrasound practices in Melbourne, Australia. It has been our practice to routinely report CL diameters for all early pregnancy scans. The data for the prospective study were generated from one site.

All examinations were performed by experienced obstetric ultrasonographers. The same model of ultrasound machines (Advanced Technology Laboratories, Bothell, WA) was used for all ultrasound scans. After confirmation of a live intrauterine pregnancy, measurements were taken to confirm gestational age. The ovaries then were identified by transvaginal B-mode ultrasonography. Once localized, color and power Doppler sonography using the low-velocity setting (10 cm/s) was applied to identify the peripheral ring of vascularity that characterizes the CL. Corpus luteum diameter was calculated as the maximum transverse diameter that was obtained after examination in two planes.

Retrospective Study

Data on CL diameter, gestation, and maternal age were collected retrospectively from the ultrasound reports of 1,806 transvaginal pregnancy ultrasound scans that were performed at 5 (+0 d) weeks' to 9 (+6 d) weeks' gestation. Women with nonviable pregnancies and cases in which one or both ovaries were not visualized were excluded from the final analysis. In this retrospective study, we did not collect data on cases of dual ovulation and excluded such women as part of our protocol, because we set out to determine laterality.

Prospective Study

Over a 6-month period, 313 transvaginal ultrasound examinations of viable pregnancies between 10 (+0 d) and 13 (+6 d) weeks were assessed prospectively for the presence of one or both ovaries and for the presence of one or more CLs. This was performed at a single practice (in Mulgrave, Victoria, Australia), at which ultrasonologists were asked to indicate formally whether they visualized these structures and to print out an image. In most cases, the indication for the scan was a nuchal translucency measurement for Down's syndrome screening.

Statistical Analysis

Because maternal age at each gestation was not normally distributed, differences in age across each gestation were assessed by using Kruskal-Wallis analysis. Analysis of variance was used to compare CL diameters across gestation. Comparisons of CL diameters observed in the retrospective (early first trimester) study and in the prospective (late first trimester) study were performed by using Student's *t*-tests. Possible differences in the distribution of CLs seen on the left and right sides between the two groups were assessed by using χ^2 analysis. Correlations between maternal age and CL diameters were performed by using regression analysis.

RESULTS

Retrospective Study at 5 to 9 Weeks' Gestation

Data were available for 1,806 pregnancies, and results are presented in Table 1. The mean (±SD) maternal age was 31.2 (5.1) years, with no differences between groups at each gestational week (P=.068). The mean CL diameter was 19.3 mm, with no significant variation in size between each gestational week (P=.118). There was a possible trend for an increase in CL diameter, from 18.5 mm at 5 weeks' gestation to the maximal size, at 6 to 8 weeks, of 19.4–19.6 mm (post hoc analysis comparing 5-wk-gestation group with 6-wk-gestation group, P=.01; *t*-test). Size then decreased at 9 weeks' gestation, to 18.9 mm. Ovulation

TABLE 1

Retrospective study of CL characteristics from ultrasound done at 5–9 weeks' gestation.

Gestation wk	CL in the left ovary, n (%)	CL in the right ovary, n (%)	CL diameter in mm, mean (±SD)[a]
5	45 (38)	73 (62)	18.5 (4.6)
6	304 (46)	340 (54)	19.6 (5.4)
7	236 (47)	261 (53)	19.2 (5.0)
8	180 (48)	194 (52)	19.4 (5.7)
9	66 (38)	107 (62)	18.9 (5.5)
Totals	831 (46)[b]	975 (54)[b]	19.3 (5.3)

[a] CL size across gestation, P=.118.
[b] Bias toward one side, P<.0001.

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occurred more commonly on the right side (54%), compared with on the left (46%; $P<.0001$). There was no correlation between maternal age and CL diameters ($P=.111$).

Prospective Study at 10 to 13 Weeks' Gestation

Data were collected for 313 women. The mean (±SD) maternal age was 30.4 (4.1) years. Both ovaries were seen in 75% (n = 237) of cases. Of the remaining 25%, only the left ovary was visible in 2% (n = 6); only the right ovary, in 3% (n = 8); and neither ovary was visualized in 20% of cases (n = 62). Of the 237 women in whom both ovaries were seen, one or more CLs were visualized in 82% (n = 194) of cases. Table 2 shows the characteristics of CL side and diameters for the 194 women in whom both ovaries were seen and at least one CL was seen. The mean CL diameter was 16.85 mm, and there was a significant decline in size across 10 to 13 weeks' gestation ($P=.003$). The CL was more commonly observed on the right side (56% vs. 44%; $P=.015$). A double ovulation on the left side was observed in two women, both of whom had twin pregnancies (dual-ovulation rate of 2/237=0.8%). An analysis of the cohort of women in whom both ovaries were seen and at least one CL was seen (n = 194) revealed no correlation between maternal age and CL diameters ($P=.879$).

Comparisons Between the Two Cohorts at 5 to 9 Weeks' and 10 to 13 Weeks' Gestation

The cohort at 10 to 13 weeks' gestation was significantly younger ($P=.006$). The mean CL diameter was significantly larger in the 5- to 9-week group than in the 10- to 13-week group ($P<.0001$). There was no statistically significant difference in the degree of right-sided CL bias that was observed in the two groups ($P=.563$).

DISCUSSION

In this study, we described the changes in CL diameters across the first trimester of pregnancy in a large series of women. The CL plays its most active role during this phase of gestation, supporting the conceptus until the luteoplacental shift that occurs at 7 to 8 weeks' gestation (1). In addition, we have for the first time examined laterality of ovulation by using the CL as a marker of ovulation. Finally, we determined prospectively how often ultrasound can locate a CL at 10 to 13 weeks' gestation.

We observed that the CL diameter remains static across 5 to 9 weeks' gestation, then declines in size afterward. This is interesting in view of the sharp rise in the luteotropin β-hCG, which occurs from the beginning of pregnancy until 10 weeks' gestation. Possible explanations for why the CL stops increasing in diameter at 5 to 6 weeks' gestation may be that it already is maximally stimulated by hCG and/or that an unknown cellular pathway down-regulates receptor responsiveness. The fact that the CL declines in size across 10 to 13 weeks' gestation, and is undetectable in 18% of cases, reflects a decline in endocrine activity.

This is the first study reporting the detection rate of the CL by transvaginal ultrasound beyond 10 weeks' gestation. The CL appears to be less readily detected at that time, compared with the case at 5 to 9 weeks' gestation (9, 10). There are many possible explanations for this: reduced vascularity may make detection more difficult, the enlarging uterus may hamper detection, or in some cases, the CL may have genuinely involuted and disappeared altogether. The fact that it cannot readily be detected disappoints us, in that we had proposed elsewhere that the zygosity of twins could be determined by noting the number of CLs seen by ultrasound (11). Although this still is possible at 5 to 9 weeks' gestation, it now appears that detection of the CL is too unreliable for this method to be used at 10 to 13 weeks' gestation, the time at which ultrasound scans are offered for nuchal translucency assessments. However, if both ovaries are visible and two CLs are seen, then the zygosity of twins may be inferred with more certainty.

Because our original aim was to determine laterality of ovulation, dual-ovulatory events were not recorded in the data that we used for the retrospective study. In hindsight, this was a missed opportunity because the incidence of dual ovulation is a fundamental question that still is unanswered. However, we did observe the number of dual-ovulation events

TABLE 2

Prospective study of CL characteristics from ultrasound scans done at 10–13 weeks' gestation.

Gestation wk	CL in the left ovary, n (%)	CL in the right ovary, n (%)	CL diameter in mm, mean (±SD)[a]
10	2 (33)	4 (66)	18.5 (2.8)
11	12 (44)	15 (56)	17.6 (3.7)
12	59 (47)	66 (53)	16.12 (3.8)
13	13 (34)	25 (66)	18.5 (3.6)
Totals	86 (44)[b]	110 (56)[b]	16.85 (3.8)

[a] CL size across gestation, $P=.003$.

[b] Bias toward one side, $P=.015$. Also note that there were 196 observations from 194 participants because two patients dual-ovulated; in each of those cases, the CL was treated as two separate observations.

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in our prospective study at 10 to 13 weeks' gestation. Among the cohort of 237 women in whom both ovaries were seen, only 2 women showed evidence of dual ovulation (0.8%). Both those occurrences resulted in twin pregnancies. This figure may be subject to some error, given that the CL was missing in 18% of ultrasound scans that were performed at 10 to 13 weeks' gestation, and no information on the use of assisted reproductive technologies was obtained. However, the ultrasound practice at which the prospective study was performed is remote from IVF centers, and it is unlikely that many of the women had had infertility treatment. It is important to note, however, that these are the first data on the incidence of dual ovulation in human beings and that they suggest that this phenomenon occurs infrequently in human beings.

By using the CL as a marker of ovulation in a large series and ending up with a figure that is remarkably similar to that of other investigators who used the dominant follicle instead (7, 8), we have indeed verified that a novel right-sided ovulation bias exists in human beings. Differences in side of ovulation exist in several other species. For example, in some birds, whales, and the chinchilla rabbit, ovulation occurs solely from the left ovary (12). Interestingly, if the left ovary is surgically removed in these species, the right ovary becomes functional.

The reasons for a right-sided ovulation bias in human beings remain unclear. A subset of our research group observed elsewhere that spontaneous dual ovulations are evenly split between both ovaries (10), suggesting that ovulation is under central endocrine control. Therefore, it simply may be that right-sided ovulatory bias arises from there being more right-sided follicles and thus, a higher probability that a dominant follicle is recruited on the right side. Support for this comes from anatomical studies of the human embryo by Mittwoch and Kirk (13), who concluded that approximately 10% more follicles are indeed present in the right human fetal ovary than in the left. The fact that right-sided ovulation occurs more frequently would suggest that if ovarian tissue needs to be taken to preserve fertility before chemotherapy, it may be better to choose tissue from the right ovary.

It is interesting to interpret the laterality of ovarian pathology in light of the bias toward right-sided ovulation. For instance, dermoid cysts more commonly are situated on the right side (48.8% right, 37.8% left, and 13.4% bilateral) (14), raising the possibility that ovulation may have some role in pathogenesis. In contrast to this, Hartage and Devesa (15) reported a large study with 25,692 observations of ovarian cancers, in which they concluded that lesions were equally distributed on both sides. In light of our data, this would be at odds with the incessant-ovulation hypothesis, which suggests that large numbers of ovulations in a lifetime may be a significant cause of ovarian cancer (16).

Our report provides data regarding the changes in CL diameter across the first trimester. It may be worthwhile to examine possible clinical applications, such as whether CL size in ectopic pregnancies provides any additional prognostic information in women undergoing methotrexate therapy, and to revisit (17) whether a small CL is associated with miscarriage in a large series. Perhaps such studies also would benefit from being performed in combination with 3-D ultrasound.

In conclusion, we have described the size of the CL across the first trimester of pregnancy in a large cohort. We have found that the CL remains static in size at 5 to 9 weeks' gestation, then declines in size from 10 to 13 weeks' gestation or may have disappeared altogether by then. Lastly, we have verified the novel fact that women ovulate more frequently from the right ovary.

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REFERENCES

1. Csapo AI, Pulkkinen MO, Ruttner B, Sauvage JP, Weist WG. The significance of the human corpus luteum in pregnancy maintenance. Am J Obstet Gynaecol 1972;112:1061–7.
2. Baerwald AR, Adams GP, Pierson RA. Form and function of the corpus luteum during the human menstrual cycle. Ultrasound Obstet Gynecol 2005;25:498–507.
3. Griffin PG, Ginther OJ. Research applications of ultrasonic imaging in reproductive biology. J Anim Sci 1992;70:953–72.
4. Miyamoto A, Shirasuna K, Hayashi KG, Kamada D, Awashima C, Kaneko E, et al. A potential use of color ultrasound as a tool for reproductive management: new observations using color ultrasound scanning that were not possible with imaging only in black and while. J Reprod Dev 2006;52:153–60.
5. Balasch J, Penarrubia J, Marquez M, Mirkin SR, Carmona F, Barry PN, et al. Ovulation and ovarian cancer. Gynecol Endocrinol 1994;8:51–4.
6. Fukuda M, Fukuda K, Yding Andersen C, Byskov AG. Contralateral selection of dominant follicle favours pre-embryo development. Hum Reprod 1996;11:1958–62.
7. Jarvela I, Nuojua-Huttunen S, Martikainen H. Ovulation side and cycle fecundity: a retrospective analysis of frozen/thawed embryo transfer cycles. Hum Reprod 2000;15:1247–9.
8. Fukuda M, Fukuda K, Yding Andersen C, Byskov AG. Characteristics of human ovulation in natural cycles correlated with age and achievement of pregnancy. Hum Reprod 2001;16:2501–7.
9. Durfee S, Frates M. Sonographic spectrum of the corpus luteum in early pregnancy: gray-scale, color and pulsed Doppler appearance. J Clin Ultrasound 1999;27:55–9.
10. Tong S, Meagher S, Vollenhoven B. Dizygotic twin survival in early pregnancy [brief communication]. Nature 2002;416:142.
11. Tong S, Vollenhoven B, Meagher S. Determining zygosity in early pregnancy by ultrasound. Ultrasound Obstet Gynaecol 2004;3: 36–7.
12. Fukuda M, Fukuda K, Yding Andersen C, Byskov AG. Right sided ovulation favours pregnancy more than left sided ovulation. Hum Reprod 2000;15:1921–6.
13. Mittwoch U, Kirk D. Superior growth of the right gonad in human foetuses. Nature 1975;257:791–2.
14. Al-Fozan H, Glassman J, Caspi B, Appelman Z, Tulandi T. Lateral distribution of ovarian dermoid cyst. J Am Assoc Gynecol Laparosc 2003;10:489–90.
15. Hartge P, Devesa S. Ovarian cancer, ovulation and side of origin. Br J Cancer 1995;71:642–3.
16. Mahdavi M, Pejovic T, Nezhat F. Induction of ovulation and ovarian cancer: a critical review of the literature. Fertil Steril 2006;85:819–25.
17. Frates MC, Doubilet PM, Durfee SM, Di Salvo DN, Laing FC, Brown DL, et al. Characteristics of the corpus luteum. Can they predict pregnancy outcome? J Ultrasound Med 2001;20:821–7.