

APPENDIX TABLE LEGENDS

Appendix Table 1. Algorithms for menstrual cycle function parameters.

Appendix Table 2. Menstrual cycle function parameters before and after bariatric surgery.

Appendix Table 1: Algorithms for Menstrual Cycle Function Parameters

Endpoints of menstrual cycle function were derived from daily vaginal bleeding diaries and urinary E₁3G and Pd3G measurements using previously described algorithms (Kassam et al., 1996; Reutman et al., 2002b; Venners et al., 2006; Rochester et al, 2009). Descriptions do not include algorithm rules for missing data.

Cycle Length & Bleeding Endpoints

- **Menses (days):** The onset of menses was the first of 2 consecutive days of bleeding, only one of which could be spotting. Menses ended with 3 or more consecutive days of nonbleeding or spotting. Intervening 1-2 day interruptions in bleeding (nonbleeding or spotting) were counted as part of menses (Reutman et al., 2002b).
- **Day of Luteal Transition (DLT) (day):** Index of ovulation when the E₁3G: Pd3G ratio begins to drop (Baird et al. 1999).
- **Menstrual Cycle Length (days):** Interval from onset of menses to day before onset of next menses.
- **Follicular Phase Length (days):** Interval from onset of menses through DLT.
- **Luteal Phase Length (days):** Menstrual cycle length minus follicular phase length.
- **Luteal Phase Length: Cycle Length (unitless):** Luteal phase length divided by menstrual cycle length.
- **Number of Bleed Days per Menses (days):** Number of days with bleeding during menses.
- **Number of Bleed Days per Interval (days):** Number of days with bleeding during menses plus adjacent bleeding days, allowing 2 day non-bleeding before or after menses.
- **Number of Bleed Days per Cycle (days):** Number of days with bleeding during the menstrual cycle.

Urinary E₁3G Endpoints:

- **Early Follicular E₁3G Level (ng/mg cr):** Arithmetic mean of E₁3G levels for cycle days 3 through 6.
- **Mid-Follicular E₁3G Level (ng/mg cr):** Arithmetic mean of E₁3G levels for cycle day 5 through day 2 before the E₁3G peak.
- **Onset of Follicular E₁3G Rise (day):** CUSUM algorithm (Schiphorst et al., 1985).
- **Rate of Follicular E₁3G Rise (ng/mg cr/day):** Slope of E₁3G levels for 3 days prior to day of E₁3G peak.
- **Days from E₁3G Rise Onset to Ovulation (days):** DLT minus onset of follicular E₁3G rise.
- **Day of E₁3G Peak (day):** Day of highest E₁3G value ≤ 3 days from DLT. If no DLT, pick highest E₁3G value.
- **3-Day Perioviatory E₁3G Peak Level (ng/mg cr):** Maximum 3-day arithmetic mean of E₁3G levels that includes the E₁3G peak.
- **Early Luteal E₁3G Level (ng/mg cr):** Arithmetic mean of E₁3G levels for days 1 through 4 after E₁3G peak.
- **Mid-Luteal E₁3G Level (ng/mg cr):** Geometric mean of E₁3G levels for days 5 and 6 after DLT (Baird et al. 1999).
- **Late luteal E₁3G Level (ng/mg cr):** Arithmetic mean of E₁3G levels for last 6 days of cycle.
- **15-Day E₁3G Level (ng/mg cr):** Arithmetic mean of E₁3G levels for 9 days before through 5 days after DLT (Venners et al., 2006).
- **28-Day E₁3G Area Under the Curve (ng/mg cr):** Sum of E₁3G levels for 13 days before through 14 days after DLT (Rochester et al., 2009).

Urinary Pd3G Endpoints:

- **Ovulatory Cycle (Y/N):** If [Pd3Gi/Pd3G Baseline] > 2 for 3 consecutive days, cycle is ovulatory; if not, cycle is anovulatory. Use Baseline 1; if not calculable, pick lowest among Baselines 2 through 4 (Kassam et al., 1996).
 - Baseline 1 (start and end menses known): Mean of cycle days 6 to 10.
 - Baseline 2 (end menses known or 35 days of sampling): Low 5-day mean.
 - Baseline 3 (end menses known): Mean of cycle days 6 to 10 of subsequent cycle.
 - Baseline 4 (end menses known): Low 5-day mean of days 1 to 14 of subsequent cycle.
- **Pd3G Baseline Level (\square g/mg cr):** Baseline selected for Anovulatory Cycle algorithm.
- **Early Follicular Pd3G Level (\square g/mg cr):** Arithmetic mean of Pd3G levels on cycle days 3 through 6.
- **Follicular Pd3G Level (\square g/mg cr):** Geometric mean of Pd3G levels from cycle day 5 through day 3 before the DLT; if no DLT, use days 6 through 10 (Baird et al. 1999).
- **Days from Ovulation to Pd3G Rise Onset (days):** Day of Pd3G rise onset minus DLT.
- **Day of Pd3G Rise (day):** First day that Pd3G levels rise > 3.5 SD above mean of previous 7 days, with next day above same limit, starting on cycle day 5.
- **Rate of Perioviatory Pd3G Rise (\square g/mg cr/day):** Slope of Pd3G levels for days 0 through 2 after DLT.
- **Early-Mid Luteal Pd3G Rise (\square g/mg cr/day):** Slope of Pd3G levels for day 3 after DLT through Pd3G peak.
- **Mid-Luteal Pd3G Level (\square g/mg cr):** Geometric mean of Pd3G levels for days 5 and 6 after the DLT (Baird et al. 1999).

Algorithms for menstrual cycle function parameters (continued)

- **Day of Pd3G Peak (day):** Day of highest Pd3G level of cycle.
- **3-Day Pd3G Peak (absolute) ($\mu\text{g}/\text{mg cr}$):** Maximum 3-day arithmetic mean of Pd3G levels that includes the Pd3G peak.
- **3-Day Pd3G Peak (relative) ($\mu\text{g}/\text{mg cr}$):** Maximum 3-day arithmetic mean of Pd3G levels that includes the Pd3G peak minus the Pd3G Baseline Level.
- **Rate of Mid-Late Luteal Pd3G Drop ($\mu\text{g}/\text{mg cr}/\text{day}$):** Slope of Pd3G levels for day of Pd3G peak through end of cycle.
- **Days from Pd3G peak to End of Cycle (days):** Cycle length minus day of Pd3G peak.
- **Luteal Pd3G Area Under the Curve 1 (ovulatory; absolute) ($\mu\text{g}/\text{mg cr}$):** Sum of Pd3G levels for day after DLT through last day of cycle.
- **Luteal Pd3G Area Under the Curve 2 (all cycles; absolute) ($\mu\text{g}/\text{mg cr}$):** Sum of Pd3G levels for day after DLT through last day of cycle, or last 14 days of anovulatory cycles.
- **Luteal Pd3G Area Under the Curve 3 (ovulatory; relative) ($\mu\text{g}/\text{mg cr}$):** Sum of Pd3G levels for day after DLT through last day of cycle minus Pd3G Baseline Level.
- **Luteal Pd3G Area Under the Curve 4 (all cycles; relative) ($\mu\text{g}/\text{mg cr}$):** Sum of Pd3G levels for day after DLT through last day of cycle, or last 14 days of anovulatory cycles, minus Pd3G Baseline Level.
- **Luteal Pd3G Area Under the Curve 5 ($\mu\text{g}/\text{mg cr}$):** Sum of Pd3G levels for 2 days before through 16 days after DLT (Rochester et al., 2009).

Urinary E₁3G: Pd3G Endpoints:

As defined above, DLT is an index of the day of ovulation, marked by the drop in the E₁3G: Pd3G ratio (Baird et al. 1999).

- **E₁3G: Pd3G Peak Level (unitless):** Value of E₁3G/ Pd3G on the day before DLT.
- **E₁3G: Pd3G DLT Level (unitless):** Value of E₁3G/ Pd3G on the DLT.
- **E₁3G: Pd3G Descent from Peak (unitless):** 3-day slope of E₁3G/ Pd3G for 0 through 2 days from peak.
- **E₁3G: Pd3G Descent from DLT (unitless):** 3-day slope of E₁3G/ Pd3G for 0 through 2 days from DLT.
- **Steepest E₁3G: Pd3G Descent (unitless):** Steepest 3-day E₁3G/ Pd3G slope starting on the DLT or the Peak.
- **Mid-Luteal E₁3G: Pd3G Level (unitless):** Geometric mean of E₁3G/ Pd3G on days 5 and 6 after DLT.

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Appendix Table 2. Menstrual Cycle Function Parameters Before (Baseline) and After Bariatric Surgery (Change from Baseline). Blue shading are significant main effects, yellow shading are significant time effects without significant main effect

Variable	Main Effect P-value	Pre-surgery	1 Month Post-Surgery		3 Month Post-Surgery		6 Month Post-Surgery		12 Month Post-Surgery		24 Month Post-Surgery	
		Mean (SD)	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value
General Endpoints												
Cycle length (days)	0.412	37.1 (24.5)	-2.5 (-9.4,4.3)	0.466	-2.9 (-8.9,3.1)	0.335	-6.0 (-11.7,-0.3)	0.038	-4.4 (-10.3,1.4)	0.138	-4.1 (-10.6,2.4)	0.212
Follicular phase (days)	0.001	22.0 (12.5)	-3.2 (-8.4,2.1)	0.234	-6.5 (-10.5,-2.4)	0.002	-8.2 (-12.3,-4.2)	0.0002	-7.9 (-12.1,-3.6)	0.0005	-8.9 (-13.9,-3.9)	0.0007
Luteal phase (days)	0.336	12.2 (2.4)	3.8 (0.4,7.2)	0.031	0.0 (-2.6,2.6)	0.990	0.8 (-1.9,3.4)	0.569	0.8 (-2.0,3.7)	0.562	0.0 (-3.4,3.4)	0.996
Luteal phase:cycle length	0.140	0.39 (0.14)	0.05 (-0.03,0.14)	0.218	0.06 (-0.01,0.12)	0.105	0.09 (0.02,0.15)	0.012	0.09 (0.02,0.16)	0.015	0.07 (-0.02,0.16)	0.103
Bleed days/menses	0.376	5.31 (1.49)	0.36 (-0.50,1.21)	0.412	-0.28 (-1.01,0.46)	0.455	-0.08 (-0.77,0.62)	0.827	0.26 (-0.45,0.97)	0.471	-0.02 (-0.79,0.76)	0.969
Bleed day/interval	0.514	5.81 (1.94)	0.36 (-0.65,1.36)	0.486	-0.26 (-1.12,0.61)	0.564	0.00 (-0.82,0.82)	0.999	0.09 (-0.75,0.93)	0.837	-0.41 (-1.33,0.51)	0.379
Bleed days/cycle	0.638	5.69 (1.83)	0.67 (-0.59,1.92)	0.298	-0.14 (-1.23,0.96)	0.806	0.18 (-0.85,1.21)	0.732	0.25 (-0.81,1.31)	0.639	-0.23 (-1.40,0.94)	0.705
E₁3G Endpoints												
Early follicular mean (ng/mg cr)	0.178	12.8 (7.5)	-2.4 (-5.6,0.8)	0.133	-2.0 (-4.5,0.5)	0.115	-0.8 (-3.3,1.7)	0.512	0.1 (-2.4,2.7)	0.912	0.8 (-2.0,3.6)	0.574
Mid follicular mean (ng/mg cr)	0.787	19.3 (9.5)	-3.1 (-11.9,5.7)	0.471	-2.1 (-8.9,4.8)	0.537	-4.6 (-11.9,2.7)	0.198	-2.9 (-10.2,4.5)	0.421	-3.34 (-11.5,4.8)	0.401
Onset of follicular rise (day)	0.983	11.7 (2.7)	-0.6 (-3.2,1.9)	0.610	-0.6 (-2.6,1.3)	0.516	-0.3 (-2.5,1.9)	0.781	-0.1 (-2.4,2.1)	0.917	-0.1 (-2.6,2.5)	0.967
Follicular rise (ng/mg cr/day)	0.955	6.40 (7.71)	-2.59 (-8.22,3.04)	0.358	-0.97 (-5.10,3.16)	0.637	-0.89 (-5.49,3.70)	0.696	-0.90 (-5.47,3.67)	0.693	-2.05 (-8.51,4.40)	0.524
E ₁ 3G rise onset → ovulation (days)	0.012	12.9 (14.7)	-3.4 (-10.0,3.3)	0.309	-7.9 (-13.2,-2.7)	0.004	-9.1 (-14.9,-3.3)	0.003	-9.6 (-15.2,-4.0)	0.001	-11.0 (-17.7,-4.2)	0.002
Day of peak (day)	0.061	19.9 (9.9)	-1.9 (-7.0,3.2)	0.461	-4.2 (-8.2,-0.3)	0.034	-5.9 (-10.2,-1.9)	0.007	-6.1 (-10.6,-1.6)	0.009	-3.6 (-9.0,1.7)	0.179
3-Day peak mean (ng/mg cr)	0.437	41.0 (26.4)	-10.1 (-27.3,7.1)	0.241	-0.2 (-11.7,11.3)	0.971	-8.9 (-22.2,4.5)	0.186	0.3 (-12.2,12.8)	0.959	-12.0 (-32.3,8.3)	0.239
Early luteal mean (ng/mg cr)	0.867	31.5 (21.2)	-0.7 (-7.7,6.4)	0.845	-1.2 (-6.8,4.5)	0.682	-3.9 (-10.4,2.7)	0.243	-2.0 (-8.3,4.3)	0.531	-4.1 (-13.1,4.9)	0.366
Mid luteal mean (ng/mg cr)	0.404	24.0 (16.8)	5.0 (-5.7,15.7)	0.352	-2.5 (-11.0,6.0)	0.554	-4.4 (-12.5,3.7)	0.276	-5.9 (-14.4,2.5)	0.161	-5.2 (-16.3,6.0)	0.354
Late luteal mean (ng/mg cr)	0.643	15.5 (10.1)	2.7 (-2.0,7.4)	0.249	1.3 (-2.2,4.8)	0.470	0.9 (-2.5,4.3)	0.590	2.8 (-1.0,6.6)	0.140	2.5 (-2.1,7.1)	0.280
15-day mean (ng•day/mg cr)	0.309	27.7 (17.2)	-5.8 (-11.5,0.0)	0.050	-4.6 (-9.1,-0.1)	0.047	-3.5 (-8.1,1.1)	0.137	-3.2 (-7.9,1.5)	0.173	-3.5 (-9.5,2.6)	0.253
28-day AUC (ng•day/mg cr)	0.515	565 (338)	-86 (-202, 31)	0.146	-22 (-104,60)	0.593	9 (-72,90)	0.821	15 (-68,99)	0.714	-38 (-137,61)	0.442
Pd3G Endpoints												
Ovulatory cycles (%)	0.177	90.0 (30.5)	9.90 (-2.4,22.3)	0.114	10.0 (-0.4,20.5)	0.06	10.1 (0.2,20.0)	0.046	10.0 (-0.5,20.8)	0.061	0.1 (-13.1,13.3)	0.984
Baseline mean (µg/mg cr)	0.858	1.30 (0.88)	0.03 (-0.34,0.39)	0.883	0.10 (-0.19,0.40)	0.487	0.12 (-0.16,0.41)	0.391	-0.06 (-0.37,0.25)	0.696	0.07 (-0.30,0.44)	0.695
Early follicular mean (µg/mg cr)	0.023	1.52 (0.91)	1.11 (0.38,1.85)	0.004	0.39 (-0.18,0.97)	0.172	0.12 (-0.46,0.70)	0.681	-0.14 (-0.73,0.45)	0.636	0.18 (-0.46,0.82)	0.572
Mid follicular mean (µg/mg cr)	0.029	1.36 (0.86)	0.44 (0.12,0.77)	0.009	0.13 (-0.14,0.40)	0.334	-0.07 (-0.34,0.21)	0.632	-0.08 (-0.37,0.21)	0.597	0.11 (-0.21,0.41)	0.503
Ovulation → Pd3G rise onset (days)	0.608	1.20 (1.55)	0.46 (-1.32,2.23)	0.601	-0.41 (-1.60,0.78)	0.489	0.52 (-0.70,1.73)	0.386	0.12 (-1.08,1.33)	0.835	-0.50 (-2.08,1.08)	0.521

Menstrual Cycle Function Parameters Before (Baseline) and After Bariatric Surgery (Change from Baseline). Blue shading are significant main effects, yellow shading are significant time effects without significant main effect (continued)

Onset of luteal rise (day)	0.213	19.5 (10.0)	1.5 (-5.0,7.9)	0.645	-2.9 (-7.4,1.6)	0.202	-4.0 (-8.7,0.7)	0.089	-4.4 (-9.1,0.2)	0.060	-4.8 (-11.1,1.4)	0.123
Luteal day 0→2 rise (µg/mg cr/day)	0.949	1.00 (1.14)	0.37 (-0.41,1.14)	0.345	0.12 (-0.48,0.73)	0.688	-0.01 (-0.65,0.63)	0.979	0.14 (-0.50,0.78)	0.666	0.14 (-0.65,0.94)	0.717
Luteal day 3→peak rise (µg/mg cr/day)	0.061	1.57 (2.09)	-0.50 (-2.22,1.22)	0.562	-0.37 (-1.77,1.03)	0.595	0.37 (-0.99,1.74)	0.582	0.26 (-1.21,1.72)	0.725	2.47 (0.63,4.31)	0.010
Luteal day 5-6 mean (µg/mg cr)	0.078	11.0 (7.1)	-2.5 (-6.3,1.3)	0.195	1.1 (-2.0,4.1)	0.473	-1.3 (-4.2,1.6)	0.370	-0.2 (-3.2,2.8)	0.895	3.8 (-0.2,7.8)	0.059
Day of peak	0.002	29.8 (8.7)	-4.3 (-9.0,0.3)	0.065	-6.7 (-10.5,-3.0)	0.0008	-7.2 (-11.0,-3.3)	0.0005	-6.8 (-10.7,-2.9)	0.0009	-9.2 (-13.9,-4.5)	0.0003
3-day peak mean (µg/mg cr)	0.400	10.7 (7.2)	-0.4 (-3.6,2.8)	0.817	2.0 (-0.6,4.6)	0.134	0.9 (-1.9,3.7)	0.517	1.9 (-0.8,4.6)	0.156	3.0 (-0.8,6.8)	0.114
3-day peak mean - base (µg/mg cr)	0.171	9.17 (6.94)	-1.38 (-4.75,1.99)	0.413	2.57 (-0.04,5.18)	0.054	0.86 (-1.86,3.57)	0.526	2.05 (-0.69,4.79)	0.138	2.61 (-1.07,6.30)	0.159
Rate of late luteal drop (µg/mg cr/day)	0.011	-1.64 (1.04)	0.45 (-0.44,1.34)	0.314	-0.58 (-1.27,0.11)	0.098	0.34 (-0.31,1.00)	0.297	-0.09 (-0.82,0.65)	0.811	-1.38 (-2.40,-0.35)	0.010
Pd3G peak → menses (days)	0.639	4.53 (2.29)	0.05 (-6.51,6.60)	0.988	1.52 (-3.66,6.70)	0.558	0.32 (-4.96,5.60)	0.904	4.10 (-1.29,9.48)	0.133	3.36 (-3.57,10.29)	0.335
Luteal AUC 1 (µg•day/mg cr)	0.301	93.8 (63.0)	-9.2 (-51.4,33.0)	0.659	29.8 (-0.2,59.9)	0.052	3.7 (-25.3,32.7)	0.796	20.1 (-10.0,50.2)	0.182	5.5 (-36.7,47.7)	0.792
Luteal AUC 2 (µg•day/mg cr)	0.108	87.0 (65.1)	-9.1 (-49.4,31.2)	0.647	34.8 (7.3,62.3)	0.015	6.3 (-21.1,33.7)	0.643	22.6 (-6.0,51.1)	0.117	-2.0 (-38.3,34.3)	0.912
Luteal AUC 3 (µg•day/mg cr)	0.438	80.0 (58.7)	-16.9 (-63.2,29.4)	0.462	26.4 (-6.6,59.3)	0.112	0.9 (-31.2,33.0)	0.954	13.7 (-19.7,47.0)	0.408	14.8 (-30.2,59.8)	0.506
Luteal AUC 4 (µg•day/mg cr)	0.237	74.0 (60.2)	-17.5 (-61.7,26.7)	0.425	31.8 (1.6,62.0)	0.040	4.2 (-26.1,34.4)	0.781	16.7 (-14.8,48.1)	0.287	3.7 (-35.4,42.9)	0.846
Luteal AUC 5 (µg•day/mg cr)	0.136	104 (69)	-10 (-48,28)	0.589	25 (-3,53)	0.077	0 (-28,27)	0.982	27 (-3,56)	0.078	21 (-14,56)	0.226
E₁3G: Pd3G Endpoints												
Peak level	0.242	42.5 (40.2)	-10.6 (-21.6,0.4)	0.058	-3.7 (-12.6,5.1)	0.402	2.9 (-6.1,11.9)	0.519	1.0 (-8.5,10.4)	0.837	-3.4 (-14.8,8.0)	0.548
DLT level	0.014	29.7 (22.1)	-13.1 (-20.9,-5.4)	0.001	-2.8 (-9.3,3.6)	0.385	-1.5 (-7.8,4.7)	0.621	-0.1 (-6.8,6.6)	0.977	-9.1 (-17.3,-0.9)	0.030
Slope from peak	0.858	-11.9 (14.4)	2.2 (-3.2,7.6)	0.413	1.0 (-3.3,5.4)	0.640	-1.2 (-5.6,3.2)	0.582	0.0 (-4.7,4.7)	0.999	-0.3 (-5.7,5.1)	0.906
Slope from DLT	0.016	-9.89 (7.81)	5.24 (1.81,8.68)	0.003	-0.18 (-2.95,2.59)	0.898	0.25 (-2.50,3.01)	0.856	0.11 (-2.73,2.95)	0.939	3.55 (0.12,6.99)	0.043
Steepest slope	0.709	-13.16 (14.53)	3.32 (-1.83,8.46)	0.202	-0.25 (-4.38,3.89)	0.905	-1.11 (-5.17,2.95)	0.585	-0.35 (-4.71,4.02)	0.874	0.50 (-4.63,5.63)	0.846
Luteal day 5-6 level	0.670	3.77 (5.49)	0.30 (-1.89,2.50)	0.781	-0.95 (-2.66,0.76)	0.270	-0.88 (-2.58,0.82)	0.305	-1.06 (-2.86,0.75)	0.246	-1.27 (-3.55,1.02)	0.271
Creatinine (mg/ml)	<0.0001	1.13 (0.35)	1.16 (0.87,1.46)	<0.0001	0.94 (0.64,1.24)	<0.0001	0.58 (0.27,0.89)	0.0004	0.40 (0.08,0.72)	0.0151	0.13 (-0.23,0.49)	0.47