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Are the pituitary gonadotrophins determinants of complete molar pregnancy? An investigation using the method of least squares

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Summary

Objective: To look for a relationship between the maternal age-specific incidence of complete molar pregnancy and the age-specific mid-follicular levels of circulating follicle stimulating hormone and luteinizing hormone.

Design: Calculation of correlation coefficients between the incidence of complete mole and the circulating levels of follicle stimulating hormone and luteinizing hormone using the method of least squares.

Setting: England and Wales.

Participants: All mothers between 23 and 49 years delivering in England and Wales between 2000 and 2009 inclusive and a sample of women between 23 and 49 years from Sheffield (1987).

Main outcome measures: The bivariate correlation coefficients between the incidence of complete mole and the mid-follicular plasma levels of the pituitary gonadotrophins.

Results: Exponential correlation between the incidence of complete mole and mid-follicular plasma follicle stimulating hormone, $r = 0.965$, $r^2 = 0.932$.

Linear correlation between the incidence of complete mole and mid-follicular plasma luteinizing hormone, $r = 0.972$, $r^2 = 0.944$.

Multivariate exponential regression between the incidence of complete mole and the combination of follicle stimulating and luteinizing hormones. This does not improve the prediction of the incidence of complete mole and it shows that luteinizing hormone is not a significant predictor of the incidence of complete mole in the presence of follicle stimulating hormone.

Conclusions: There is a strong positive exponential correlation between the maternal age-specific incidence of complete mole in England and Wales and the age-related mid-follicular levels of follicle stimulating hormone in a sample of English women.

Keywords

determinants of complete hydatidiform mole, follicle stimulating hormone, luteinizing hormone

Introduction

Every complete mole is the result of a monospermic or dispermic fertilization of an empty ovum. There are only rare exceptions to this rule.[1] Ovulation with follicular maturation and completion of meiosis I is driven by follicle stimulating hormone (FSH) and luteinizing hormone (LH) whose plasma levels vary according to the stage of the menstrual cycle and maternal age.[2] The maternal age-specific incidence of complete mole (ICM) is bimodal with a minor peak in teenagers, a minimum in the mid-thirties and a higher maximum in mothers over 40 years. This pattern is universal but remains unexplained.[3] My hypothesis is that the maternal age-related variation in the ICM is determined by the age-related changes in the circulating levels of the pituitary gonadotrophins and I have investigated this by using the published work of Elizabeth Lenton and Philip Savage to search for correlations between the ICM in England and Wales and the mid-follicular levels of circulating gonadotrophins in a sample of English women.[4,5]

Subjects and methods

In 1987, Lenton examined a sample of 127 women from Sheffield, England, aged 23–49 years and measured their mid-follicular (days −10 to −5 with respect to the mid-cycle surge in LH) levels of plasma FSH and LH.[4] She expressed the results as geometric means in international units per litre (IU/L) and arranged them into 14 two-year age bands showing that the age-related rise in FSH takes place at 40–41 years, 4 years earlier and proportionally greater than the rise in LH. The use of mid-follicular samples excluded menstrual variation and ensured that any changes in gonadotrophin levels were age related. Mid-follicular values of FSH are second only to the mid-cycle FSH surge and are higher than random measurements.[4]

Savage has recently published figures for the age-related risk of complete mole in England and Wales (2000–2009) for mothers between 13 and 50+ years, expressing his results as the risk of one complete mole per number of viable conceptions, including live

Table 1. Incidence of complete mole (number of complete moles per thousand viable conceptions), follicle stimulating and luteinizing hormones (international units per litre), all in two-year age bands.

Age (years)	FSH (IU/L)	LH (IU/L)	Incidence of complete mole (No. CM/1000 VC)
23	5.3	6.6	0.61
24–25	5.0	6.3	0.60
26–27	5.2	6.1	0.64
28–29	5.9	6.3	0.59
30–31	5.0	6.3	0.55
32–33	5.4	6.1	0.56
34–35	5.0	6.8	0.49
36–37	5.4	6.1	0.51
38–39	6.1	6.6	0.69
40–41	7.4	7.6	0.90
42–43	8.2	6.3	2.20
44–45	9.4	6.6	4.46
46–47	9.7	8.3	14.94
48–49	14.4	12.7	41.89

births, stillbirths, legal terminations and moles.[5] I have converted his figures to the number of complete moles per 1000 viable conceptions (ICM) for mothers between 23 and 49 years to match Lenton's data for the gonadotrophins. This maternal age range includes the lowest and the penultimate values for the ICM. The highest value for the ICM is at 50+ years but Lenton gives no matching gonadotrophin levels at this age nor for women younger than 23 years.

The data used in this study are recorded in Table 1. Correlations between the age-related ICM and the plasma gonadotrophins were sought using the method of least squares after initial examination of the data using scatter plots. Bivariate models of the ICM (dependent variable) and the FSH, and LH (explanatory variables) were constructed. Multivariate models were examined to determine whether using the gonadotrophins together improved the prediction of the ICM.

Results

The regression coefficients and equations for the exponential relationship of ICM and FSH, the linear relationship between ICM and LH and the multivariate exponential relationship between ICM and FSH combined with LH are given in Table 2. Each model accounts for at least 90% of the variance in ICM.

The best model is the exponential one linking ICM and FSH as it is consistent with the largest number of data points and has the smallest standard error. A single unit increase in FSH leads to an approximate two-thirds increase in the ICM.

The linear model of ICM and LH does not predict the lower levels of ICM accurately as it is driven largely by the two highest data points. When these two points are excluded the correlation coefficient for the first 12 points is very low, $r = 0.104$, $r^2 = 0.011$. In addition, the standard error for the full model (14 data points) is more than seven times greater than that for the exponential model of ICM and FSH.

The multivariate model does not improve the prediction of ICM and it demonstrates that LH is not a significant predictor of ICM in the presence of FSH.

Discussion

The results show that there is a positive exponential correlation between the maternal age-specific ICM in England and Wales and the circulating age-specific mid-follicular FSH in a sample of English women, and that LH is not a significant predictor of ICM in the presence of FSH.

The results from the London-based Gestational Trophoblastic Disease Centre are population based, subject to expert histological review and include every year of maternal age from menarche to menopause.[5] In addition, because of the Centre's long experience in gathering information on incident molar pregnancies it is likely that the ascertainment of moles is optimal.[5] Regrettably, the figures for FSH and LH only extend from 23 to 49 years.[4] There are no other studies of the relationship between ICM and FSH but the regression equation of Table 2 enables predictions of mid-follicular FSH to be made for English teenagers and women of 50+ (Table 3). These predictions can be tested in observational studies and are in agreement with Neely's random FSH results from Californian girls and teenagers in showing that following a childhood surge FSH levels peak at the menarche, around 14 years, and then fall during the late teens towards the levels found in young adults by Lenton.[4,6] The pattern of circulating FSH matches that of ICM, a minor peak at menarche, a minimum between 20 and 35 years and finally a major peak approaching the menopause. The hypothesis that circulating FSH is a determinant of complete mole is biologically plausible as FSH is intimately involved

Table 2. Regression coefficients for the relationships between ICM and FSH, ICM and LH, and ICM and FSH and LH combined.

Relationship	r	r^2	Standard error of estimate	Slope	Intercept	t	p
ICM and FSH	0.965	0.931	0.386	0.505	−3.249	12.719	<0.001
Exponential equation: $ICM = 0.039 \times \exp(0.505 \times FSH)$ or $FSH = \frac{[\ln ICM + 3.249]}{0.505}$							
ICM and LH	0.972	0.944	2.782	6.306	−39.484	14.230	<0.001
Linear equation: $ICM = -39.484 + 6.306\ (LH)$							
ICM and (FSH and LH)	0.965	0.932	0.400		−3.065		
	FSH:			0.539		6.255	<0.001
	LH:			−0.059		−0.444	<0.666
Exponential equation: $ICM = 0.047 \times \exp(0.539 \times FSH) \times \exp(-0.059 \times LH)$							

Table 3. Observed ICM in England and Wales with predicted mid-follicular FSH in English teenagers and women of 50 + (5).

Age (years)	Observed ICM (No. CM/1000 VC) (5)	Predicted FSH (IU/L)
13–14	2.87	8.5
15–16	1.76	7.6
17–18	1.04	6.5
19–20	0.78	5.9
21–22	0.68	5.7
50+	125.00	15.8

in oocyte and follicular maturation, including the resumption of meiosis I.[2,7]

Circulating levels of FSH are increased in cigarette smokers and show a positive correlation with the number of cigarettes smoked.[8–10] In Italy, La Vecchia has shown that the frequency of trophoblastic tumours including complete mole is doubled in smoking mothers.[11] Suggestions that the raised levels of FSH in smokers are the result of accelerated ovarian ageing are incorrect: ageing is an irreversible process but the raised FSH levels in smokers return to normal in ex-smokers and prenatal exposure to maternal smoking has no effect on FSH levels in their adult female offspring.[9] Furthermore, ovarian ageing from 13 to 35 years is not accompanied by a rising FSH (Tables 1 and 3).[4]

Studies on primates exposed to combinations of recombinant gonadotrophins (rFSH, rLH) following prolonged treatment with a gonadotrophin hormone releasing hormone antagonist (Antide) suggest that only FSH is essential for follicular growth and completion of meiosis. These findings are supported by studies on Finnish women with an inactivating point mutation in the gene for the FSH receptor who present with primary amenorrhoea associated with biopsy proven failure of oocyte and follicular maturation.[12,13] Recent studies by Gianaroli in Italy and Esther Baart in the Netherlands working in assisted conception units show that increasing the dose of rFSH to which oocytes are exposed increases the frequency of aneuploidy.[14,15] Baart's patients were in two randomly chosen groups of equal age distribution, with the higher dose group receiving 50% more rFSH than the low dose one. All embryos were biopsied and examined by fluorescent *in situ* hybridization to determine the presence of aneuploidy. There were 40% more aneuploid embryos in the high dose group, a significant difference ($p = 0.02$). It is not oocyte ageing which determines aneuploidy but the level of exposure to FSH so that when FSH peaks at menarche and approaching the menopause there is a probable increase in the frequency of aneuploid ova with no maternal chromosomes leading to the bimodal peaks in the ICM.

Analytical epidemiological studies on cohorts of individual patients with known pre-conception mid-follicular FSH levels and subsequent determination of pregnancy outcome will be required to test this hypothesis. Such studies will be most easily conducted amongst populations with known high

frequencies of complete mole: the Japanese and the Gulf Arabs of Oman and Yemen.[3,16] In the UK, the population with the highest frequency of complete mole is the group of postmolar patients managed by Savage and his colleagues at the Trophoblastic Disease Centres in London and Sheffield.[5]

Declarations

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References

1. Seckl MJ, Sebire NJ and Berkowitz RS. Gestational trophoblastic disease. *Lancet* 2010; 376: 717–729.
2. Huang Z, Fragouli E and Wells D. Biomolecules of human female fertility – potential targets for pharmaceutical design. *Curr Pharma Des* 2012; 18: 310–24.
3. Bracken MB. Incidence and aetiology of hydatidiform mole: an epidemiological review. *Br J Obstet Gynaecol* 1987; 94: 1123–1135.
4. Lenton EA, Sexton L, Lee S and Cooke ID. Progressive changes in LH and FSH and LH:FSH ratio in women throughout reproductive life. *Maturitas* 1988; 10: 35–43.
5. Savage PM, Sita-Lumsden A, Dickson S, Iyer R, Everard J, Coleman R, et al. The relationship of maternal age to molar pregnancy incidence, risks for chemotherapy and subsequent pregnancy outcome; data for England and Wales 2000–2009. *J Obstet Gynaecol* May 2013; 33: 406–411.
6. Neely EK, Hintz RL, Wilson DM, Lee PA, Gautler T, Argente J, et al. Normal ranges for immunochemiluminometric gonadotrophin assays. *J Pediatr* 1995; 127: 40–46.
7. Zhang M, Ouyang H and Xia G. The signal pathway of gonadotrophins – induced mammalian oocyte meiotic resumption. *Mol Hum Reprod* 2009; 15: 399–409.
8. Backer LC, Rubyn CS, Marcus M, Kieszak SM and Schober SE. Serum follicle-stimulating hormone and luteinizing hormone levels in women aged 35-60 in the U.S. population: the third National Health and Nutrition Examination Survey (NHANES III, 1988-1994). *Menopause* 1999; 6: 29–35.
9. Cooper GS, Baird DD, Hulka BS, Weinberg CR, Savitz DA and Hughes CL. Follicle-stimulating hormone concentrations in relation to active and passive smoking. *Obstet Gynecol* 1995; 85: 407–411.
10. Cramer DW, Barbieri RL, Xu H and Reichardt JK. Determinants of basal follicle-stimulating hormone levels in premenopausal women. *J Clin Endocrinol Metab* 1994; 79: 1105–1109.
11. La Vecchia C, Francheschi S, Parazzini F, Fasoli M, Decarli A, Gallus G, et al. Risk factors for gestational trophoblastic disease in Italy. *Am J Epidemiol* 1985; 121: 457–464.
12. Zelinski-Wooten MB, Hutchison JS, Hess DL, Wolf DP and Stouffer RL. Follicle stimulating hormone alone supports follicle growth and oocyte development in gonadotraophin-releasing hormone antagonist-treated monkeys. *Hum Reprod* 1995; 10: 1658–1666.
13. Aittomäki K, Herva R, Stenman U-H, Juntunen K, Ylostalo P, Hovatto O, et al. Clinical features of primary ovarian failure caused by a point mutation in the follicle-stimulating hormone receptor gene. *J Clin Endocrinol Metab* 1996; 81: 3722–3726.
14. Gianaroli L, Magli MC, Cavallini G, Crippa A, Capoti A, Resta S, et al. Predicting aneuploidy in human oocytes: key factors which affect the meiotic process. *Hum Reprod* 2010; 25: 2374–2386.
15. Baart EB, Martini E, Eijkmans MJ, Van Opstal D, Beckers NG, Verhoeff A, et al. Milder ovarian stimulation for in-vitro fertilization reduces aneuploidy in the human preimplantation embryo: a randomised controlled trial. *Hum Reprod* 2007; 22: 980–988.
16. Graham IH, Fajardo AM and Richards RL. Epidemiological study of complete and partial hydatidiform mole in Abu Dhabi: influence of maternal age and ethnic group. *J Clin Pathol* 1990; 43: 661–664.