UC Irvine
UC Irvine Previously Published Works

Title

A Sex-Specific Test of Selection in Utero

Permalink

Journal

ISSN

Authors

Catalano, Ralph A.
Saxton, Katherine
Bruckner, Tim
et al.

Publication Date

Peer reviewed

A Sex-Specific Test of Selection *in Utero*

Ralph A. Catalano[a], **Katherine Saxton**[a], **Tim Bruckner**[a], **Sidra Goldman**[a], and **Elizabeth Anderson**[a]

a*University of California at Berkeley School of Public Health Berkeley, CA, USA 94720-7360*

Abstract

We find support for the hypothesis that changes in the monthly odds of a twin among live-born males predict subsequent and opposite changes in the odds of a twin among live-born females. The hypothesis arises from the long standing argument that natural selection has conserved mechanisms by which pregnant women in stressed populations spontaneously abort fetuses least likely to yield grandchildren. Previous attempts to empirically test this argument focus almost entirely on males. We contribute to the literature by showing that, consistent with the logic of natural selection, maternal adaptations to environmental changes likely have effects on the survival of both male and female conceptuses and fetuses.

Keywords

Natural selection; fitness; multiple births; pregnancy

Introduction

Research suggests that as many as 70% of human conceptions end without live births (Boklage, 1990). Mechanisms contributing to this loss presumably include selection *in utero* or the spontaneous abortion of conceptuses least likely to yield grandchildren (Trivers and Willard, 1973). This screening mechanism assumes a ranking of gestations on expected yield of grandchildren as well as a value on that ranking below which women spontaneously terminate pregnancies (Catalano and Bruckner, 2006; Forbes, 1997). A gestation's rank reflects, at least in part, the probability that the infant, if born, would survive to reproductive age. Male conceptuses, for example, disproportionately fall below the criterion for abortion because, if born, they more likely die before reproductive age than females despite receiving more maternal investment (Wells, 2000).

The neonatal environment affects the likelihood of offspring surviving to reproductive age. The argument for selection *in utero* acknowledges this circumstance by positing that natural selection has conserved mechanisms by which women change the criterion for spontaneous abortion to reflect environmental conditions. Assuming a ranking of high to low, the criterion would fall during relatively benign times and rise in stressful times (Trivers and Willard, 1973).

Corresponding author: Ralph Catalano, Ph.D., School of Public Health, UC Berkeley, 50 University Hall, Berkeley, CA 94720-7360 Phone: 510-642-3103 Fax : 510-588-4715 Email: E-mail: rayc@berkeley.edu.

Selection *in utero* suggests the hypothesis that the ratio of male to female live births (i.e., secondary sex ratio) will decline among birth cohorts in gestation during stressful times. Tests of this hypothesis report that the secondary sex ratio varies inversely over time with such population stressors as economic contraction (Catalano and Bruckner, 2005), weather extremes (Helle et al., 2008), political upheaval (Kemkes, 2006), natural and human-made environmental disasters (Fukuda et al., 1998; Lyster, 1974), and terrorist events (Catalano et al., 2006; Catalano et al., 2005a). These findings converge with the epidemiologic literature that reports fewer than expected male births among women subjected to stressful life events (Obel et al., 2007) and with reports of lower secondary sex ratios in birth cohorts in gestation at times when the incidence of treated anxiety and depression among women increases (Catalano et al., 2005b).

While consistent with the theory of selection *in utero*, these findings ignore that ratios can vary as much from change in their denominators as in their numerators. This oversight persists despite the fact that research reports that characteristics of daughters as well as of sons predict yield of grandchildren across mothers (Gabler and Voland, 1994; Lummaa et al., 2001). The work estimates not only the survival of children under more or less stressful circumstances (Lummaa et al., 2001), but also the yield of grandchildren to deliveries of singletons of both sexes and to mixed and same-sex twins (Gabler and Voland, 1994). Based on these estimates we offer a sex-specific test of selection *in utero*. More specifically, we test the hypothesis that changes in the monthly odds of a twin among live-born males predict subsequent and opposite changes in the odds among live-born females.

Yield of Grandchildren

The literature includes, to our knowledge, only one accounting of grandchildren by delivery type (i.e., sex by singleton or twin status) before social reforms and medical innovations decreased infant and child mortality in the emerging industrial nations. Based on a small population in Germany observed from the mid-18th to mid-19th centuries, Gabler and Voland (1994) inferred that female-female twin sets yield the most grandchildren while male-male twin deliveries yield the fewest. These findings converge with others describing survival of male and female twins to reproductive age in a Finnish population thought to occupy more and less stressful environments during the same century (Lummaa et al., 2001).

Estimates of fitness by delivery type would ideally reflect not only the yield of grandchildren per type, but also the cost to the mother of sustaining each type to reproductive age. Estimating such costs in preindustrial societies presents conceptual and empirical challenges. Helle and colleagues (Helle et al., 2002) used mother's lifespan in the Sami people of Finland from 1640 to 1870 as an indicator of the biological costs of raising males and females. They report an inverse association between the number of sons and maternal life expectancy but a positive association between lifespan and number of daughters. Lumaa (2001) suggests interbirth interval (i.e., time between deliveries) as a gauge of maternal costs in preindustrial (i.e., 1752 - 1850) Finland. Women who gave birth to male-male twins had the longest interbirth interval followed by male singletons, female singletons, and, finally, female-female twins. Using mother's lifespan and interbirth interval as indicators of maternal investment yields a ranking from high to low that matches the ranking of delivery type by yield of grandchildren. The convergence of these rankings suggests that male and female twins occupy opposing positions at the extremes of sex-specific rankings on fitness.

The opposing ranks of female and male twin deliveries imply opposite effects of selection *in utero* on the odds of a twin among male and female birth cohorts. As shown in figure 1, a rising criterion for spontaneous abortion would cull male twins before male singletons because male twins disproportionately inhabit the low end of the ranking of deliveries on fitness. The odds

of a male twin should decline under such circumstances because the numerator (i.e., number of male twins from any twin set) of the ratio used to calculate odds declines more than the denominator (i.e., number of male singletons).

A rising criterion for spontaneous abortion would, obversely, cull female singletons before female twins because the former fall below the latter on fitness. The odds of a female twin should rise under such circumstances because the denominator declines more than the numerator. These opposing effects would induce a negative association over time between the sex-specific odds of twins.

Most spontaneous abortions occur early in gestation, but those among females appear more concentrated in the first trimester than those among males (Boklage, 2005; Evdokimova et al., 2000). Fetal loss of both sexes declines after the first trimester and then peaks again between the 16th to 20th week (Goldhaber and Fireman, 1991). Males predominate in this second peak, possibly reflecting their greater reactivity to maternal corticosteroids (Owen and Matthews, 2003).

This difference implies that opposing selection triggered by maternal adaptation to environmental circumstances would manifest itself in birth cohorts such that the odds of a male twin would change before opposite changes in the odds of a female twin. This pattern would emerge because the stress-induced culling of males would occur nearer in time to birth than the stress-induced culling of females.

We test for associations between the odds of male and female twins by applying time-series methods to 204 months (i.e., 1989 through 2005) of data from California, home to 37 million Americans of diverse ethnicity who yield roughly 13% of all births in the United States. We predict an inverse association consistent with the opposite-effects hypothesis. This association should appear such that changes in the odds of a male twin precede opposite changes in the odds of a female twin.

Phenomena other than stress-induced abortion will, of course, affect the odds of twins in birth cohorts. Intuition and research suggest, for example, that variability over time in the efficacy of medical procedures such as assisted reproductive technology and neonatal intensive care would change the likelihood of conceiving twins (Reynolds et al., 2003) or of saving very small twins who account for a disproportionately large share of preterm deliveries (Kiely, 1998). Medical innovations typically affect both sexes either at conception or delivery and should, therefore, induce similar changes in the odds of twins of both sexes in the same birth cohorts. Early culling of chromosomally abnormal twins of both sexes may, moreover, contribute to such a positive association in birth cohorts. For all these reasons we test for a positive correlation in male and female cohorts born at the same time as well as for our hypothesized association in which changes in the odds of a male twin precede opposite changes in the odds of female twin.

Methods

Data

We acquired birth data for the 17 years from 1989 (first in the series of years with consistent classification rules) through 2005 (most recent year of available data at time of our analyses) from the Maternal and Child Health Branch of the State of California Department of Health Services. We constructed monthly sex-specific odds of twinning by dividing the number of male or female live-born twins in a monthly birth cohort by singleton live births of the same sex in the cohort.

Analyses

We test the hypothesis that movements away from statistically expected values in the odds of a male twin precede opposite movements from expected values in the odds a female twin. Researchers typically assume that, under the null hypothesis, the statistically expected value of a variable is its mean. The odds of twinning, however, may exhibit trends, cycles, or the tendency to remain elevated or depressed, or to oscillate, after high or low values. These patterns, referred to collectively as autocorrelation, complicate tests such as ours because the expected value of an autocorrelated series is not its mean.

Researchers dating to Fisher (Fisher, 1921) have overcome autocorrelation by "decomposing" time series into predictable and residual components. The residual components of each series, which become the analyzed variables, have no autocorrelation thereby precluding spurious associations due to shared temporal patterning.

We implemented Fisher's approach through the following steps.

1. We used Dickey-Fuller (Dickey and Fuller, 1979) and Box-Jenkins methods (Box et al., 1994) to decompose the monthly odds of a twin among live male and female births into statistically expected and unexpected components. These methods employ iterative model building to identify and express autocorrelation in time series as a function of autoregressive and moving average processes. The estimated values of the best-fitting model can be thought of as the expected component of the modeled series while the differences between the observed and estimated values are the unexpected component. The general Box-Jenkins equation for data such as ours is as follows.

$$\nabla Z_t = C + \frac{(1 - \theta B^q)}{(1 - \phi B^p)} a_t$$

[1]

∇ is the difference operator that indicates the variable has been differenced (i.e., values at month t subtracted from values at month t+1) to remove secular trends.

Z_t are the odds of a twin among male or female infants born in California during month t.

C is a constant.

θ is the moving average parameter.

φ is the autoregressive parameter.

B is the value of the variable at month t-q for moving average and t-p for autoregressive processes.

a_t is the residual, or unexpected value, at month t.

2. We specified a regression equation with the residual series from the equation derived in step 1 for females as the dependent variable and the residual series for males as the predictor. We specified the odds of a male twin in the synchronous configuration (i.e., values occurring in the same month as the odds of female twin) as well as preceding the odds among females by 1, 2, and 3 months. We hypothesize that the coefficient for the independent variable leading the dependent variable by 2 months will fall below the 95% confidence interval (2-tailed test). The possibility, discussed above, that medical innovations and early culling also affect the likelihood of twinning

predicts a statistically significant positive coefficient in the synchronous
configuration.

3. We estimated the equation specified in step 2 and inspected the residuals for
autocorrelation to ensure that the parameters were efficient. We added Box-Jenkins
parameters to the equation if needed and estimated the test equation again.

Results

The 9,426,527 live births in California over the test period included 115,668 male, and 116,688
female, twins. The monthly odds of a twin among male live births ranged from .0187 to .0335
with a mean of .0247 over the 204 test months. Among females the odds ranged from .0198
to .0356 with a mean of .0261.

The observed values for females showed increasing variability over time requiring us to
transform the odds to their natural logarithms (i.e., logits) and to similarly transform the odds
for males. Figures 2 and 3 show the results of the first and second steps above in which we
separately estimated the expected values of the logit of a male and female twin over the 204
test months.

Table 1 shows the best fitting Box-Jenkins equations for the two series. Both series trend
upward thereby requiring us the take their first differences (i.e., ∇ parameter in equation 1).
Both, following differencing, showed weak oscillation implying further adjustment with
moving average parameters (i.e., θ parameter in equation 1).

Table 2 shows the estimated values for the test equation in which we used the residuals of the
Box-Jenkins equation, shown in table 1, for males to predict the residuals of the Box-Jenkins
equation, also shown in table 1, for females. Table 2 shows estimates with and without the
non-significant (i.e., p> .05; 2-tailed test) parameter for male odds 3 months before female
odds. The findings support our hypothesis that the likelihood of a twin among female live births
varies inversely with the likelihood of a twin among male live births approximately 2 months
earlier. The results also support the expectation that the likelihood of a twin among live births
of both sexes vary positively in the same monthly birth cohorts.

The equation accounts for 15.5% of the variance in the dependent variable. The parameter for
the 2nd prior month implies that an unexpected 1% change in the odds of twin male birth
precedes an unexpected and opposite change of approximately .16% in the odds of twin female
birth.

Discussion

Consistent with sex specific selection *in utero*, we found that movements away from expected
values in the odds of twinning among males in monthly birth cohorts predicted opposite
movements in the odds among females 2 months later. We believe our argument and findings
contribute to the literature concerned with selection *in utero* (Catalano, 2003; Catalano and
Bruckner, 2005; Catalano et al., 2005a; Catalano et al., 2006; Helle et al., 2008) in at least two
ways. First, we make clear that nothing in the logic of natural selection justifies the
preoccupation in the existing literature with spontaneous abortion of male conceptuses. The
benefits in yield of grandchildren of selection *in utero* appear sufficient to speculate that natural
selection would conserve mechanisms that affect survival of conceptuses of both sexes.

Second, our analyses improve on tests that dominate the empirical literature concerned with
selection *in utero* among humans. These tests cite declines in the ratio of male to female live
births after stressors on the population as evidence that women have spontaneously aborted

male conceptuses. We believe that our tests demonstrate that changes in the secondary sex ratio can reflect the spontaneous abortion of females as well as of males.

The high frequency of male twins among least fit deliveries implies that a movement in the abortion criterion across these low ranks will affect the odds of a male twin more than of a female twin. Our finding that a 1% change in the odds of male twinning predicts a subsequent and opposite change of .16% in female twinning reflects this circumstance.

The literature concerned with selection *in utero* implies hypotheses other than those that we tested. The work focusing on secondary sex ratios, for example, implies that among women exposed to the same transient stressor, those who have no children during the exposure eventually have more grandchildren than those who, in that period, have frail sons, but fewer than those who have frail daughters. We know of no data that allow a test of these predictions. Our test, therefore, probably provides the strongest evidence derivable from currently available data.

Limitations of our approach include that we cannot know if our results describe times and places other than California over the 204 months analyzed. Only replication can establish the external validity of our findings. We, moreover, caution against using our results to estimate the culling of either male twins or female singletons in response to specific population stressors (e.g., economic downturns, terrorist attacks). Such estimates await "second generation" research into sex specific dose response to environmental stressors.

Our hypothesis arose from reports that giving birth to twins affected the number of grandchildren left by women residing in Western Europe before the industrial age. That effect, moreover, differed by sex such that male twins yielded the fewest, while female twins yielded the most, grandchildren. We do not know whether having twins in contemporary societies continues to affect the yield of grandchildren. Cultural preferences — delayed childbearing and the desire for fewer children, to name but two — could negate any effect. Indeed, we do not know how much culture contributed to the fitness of twins during the period we studied and, if it did, whether that contribution amplified or reduced the contribution of the biological determinants of fitness. Our findings suggest, however, that stress-induced selection *in utero* continues to affect the number and characteristics of males and females in contemporary populations.

Acknowledgments

References

Boklage CE. The survival probability of human conceptions from fertilization to term. Int J Fert 1990;35:75–94.

Boklage CE. The epigenetic environment: secondary sex ratio depends on differential survival in embryogenesis. Hum Reprod 2005;20:583–7. [PubMed: 15618256]

Box, G.; Jenkins, G.; Reinsel, G. Time Series Analysis: Forecasting and Control. Prentice Hall; London: 1994.

Catalano RA. Sex ratios in the two Germanies: a test of the economic stress hypothesis. Hum Reprod 2003;18:1972–5. [PubMed: 12923159]

Catalano RA, Bruckner T. Economic antecedents of the Swedish sex ratio. Soc Sci Med 2005;60:537–43. [PubMed: 15550302]

Catalano R, Bruckner T. Secondary sex ratios and male lifespan: damaged or culled cohorts. Proc Natl Acad Sci U S A 2006;103:1639–43. [PubMed: 16432236]

Catalano R, Bruckner T, Gould J, Eskenazi B, Anderson E. Sex ratios in California following the terrorist attacks of September 11, 2001. Hum Reprod 2005a;20:1221–7. [PubMed: 15734763]

Catalano R, Bruckner T, Hartig T, Ong M. Population stress and the Swedish sex ratio. Paediatr Perinat Epidemiol 2005b;19:413–20. [PubMed: 16269068]

Catalano R, Bruckner T, Marks AR, Eskenazi B. Exogenous shocks to the human sex ratio: the case of September 11, 2001 in New York City. Hum Reprod 2006;21:3127–31. [PubMed: 16936298]

Dickey D, Fuller W. Distribution of the estimators for autoregressive time series with a unit root. J Am Stat Assoc 1979;74:427–31.

Evdokimova VN, Nikitina TV, Lebedev IN, Sukhanova NN, Nazarenko SA. About the sex ratio in connection with early embryonic mortality in man. Russian Journal of Developmental Biology 2000;31:204–210.

Fisher RA. Studies in crop variation: An examination of the yield of dressed grain from Broadbalk. J Agri Sci 1921;11:107–35.

Forbes LS. The evolutionary biology of spontaneous abortion in humans. Trends in Ecology and Evolution 1997;12:446–450.

Fukuda M, Fukuda K, Shimizu T, Moller H. Decline in sex ratio at birth after Kobe earthquake. Hum Reprod 1998;13:2321–2. [PubMed: 9756319]

Gabler S, Voland E. Fitness of twinning. Hum Biol 1994;66:699–713. [PubMed: 8088755]

Goldhaber MK, Fireman BH. The fetal life table revisited: spontaneous abortion rates in three Kaiser Permanente cohorts. Epidemiology 1991;2:33–9. [PubMed: 2021664]

Helle S, Helama S, Jokela J. Temperature-related birth sex ratio bias in historical Sami: warm years bring more sons. Biol Lett 2008;4:60–2. [PubMed: 18042510]

Helle S, Lummaa V, Jokela J. Sons reduced maternal longevity in preindustrial humans. Science 2002;296:1085. [PubMed: 12004121]

Kemkes A. Secondary sex ratio variation during stressful times: the impact of the French revolutionary wars on a German parish (1787-1802). Am J Hum Biol 2006;18:806–21. [PubMed: 17039472]

Kiely JL. What is the population-based risk of preterm birth among twins and other multiples? Clin Obstet Gynecol 1998;41:3–11. [PubMed: 9504218]

Lummaa V. Reproductive investment in pre-industrial humans: the consequences of offspring number, gender, and survival. Proc R Soc Lond B 2001;268:1977–1983.

Lummaa V, Jokela J, Haukioja E. Gender difference in benefits of twinning in pre-industrial humans: boys did not pay. The Journal of Animal Ecology 2001;70:739–746.

Lyster WR. Altered sex ratio after the London smog of 1952 and the Brisbane flood of 1965. J Obstet Gynaecol Br Commonw 1974;81:626–31. [PubMed: 4423712]

Obel C, Henriksen TB, Secher NJ, Eskenazi B, Hedegaard M. Psychological distress during early gestation and offspring sex ratio. Hum Reprod 2007;22:3009–12. [PubMed: 17768170]

Owen D, Matthews SG. Glucocorticoids and sex-dependent development of brain glucocorticoid and mineralocorticoid receptors. Endocrinology 2003;144:2775–84. [PubMed: 12810530]

Reynolds MA, Schieve LA, Martin JA, Jeng G, Macaluso M. Trends in multiple births conceived using assisted reproductive technology, United States, 1997-2000. Pediatrics 2003;111:1159–1162. [PubMed: 12728130]

Trivers RL, Willard DE. Natural selection of parental ability to vary the sex ratio of offspring. Science 1973;179:90–2. [PubMed: 4682135]

Wells JC. Natural selection and sex differences in morbidity and mortality in early life. J Theor Biol 2000;202:65–76. [PubMed: 10623500]
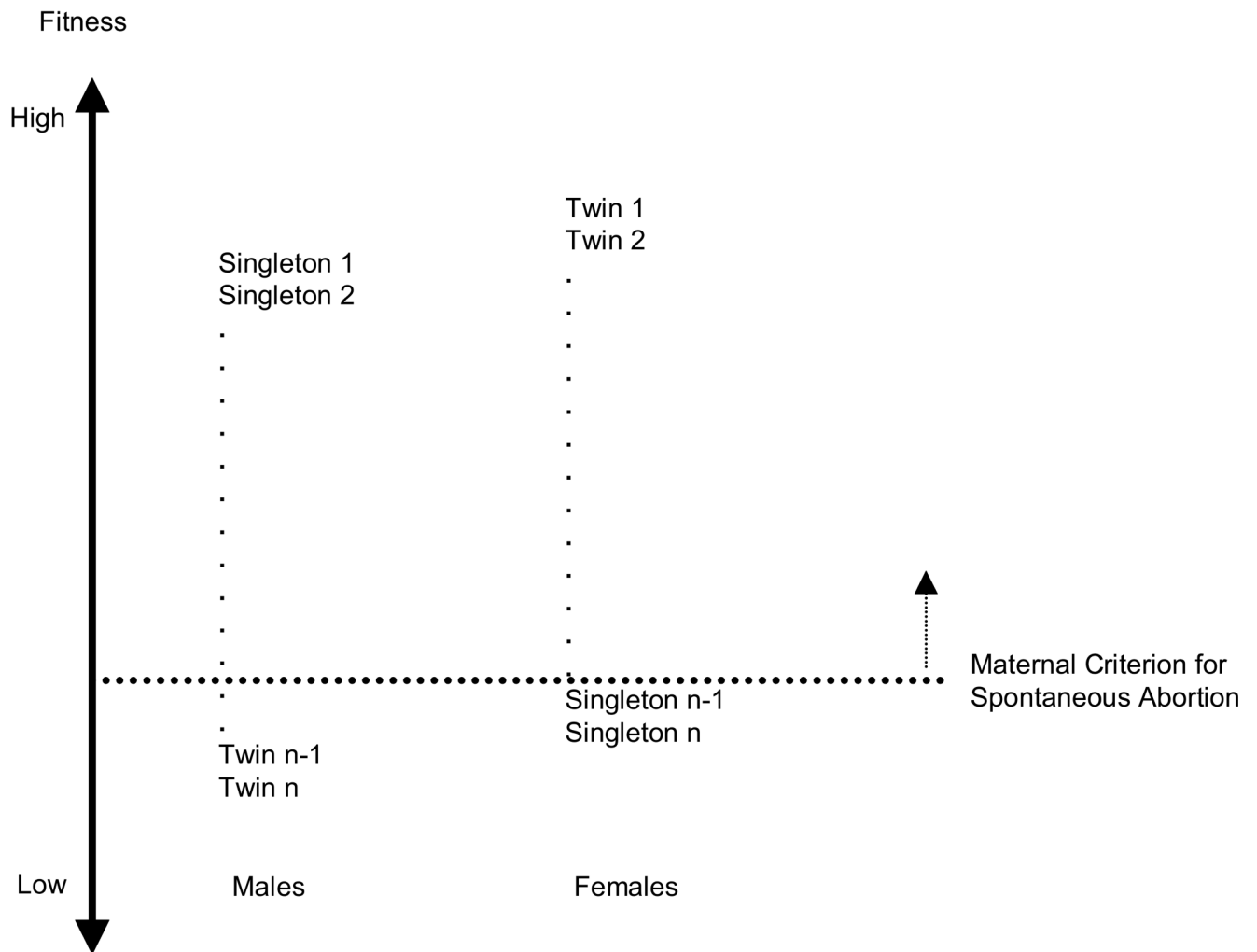
Figure 1.
Stylized representation of maternal criterion for spontaneous abortion and of fetuses ranked
by fitness. Rising criterion disproportionately culls male twins and female singletons thereby
lowering the odds of male twin while increasing the odds of a female twin.
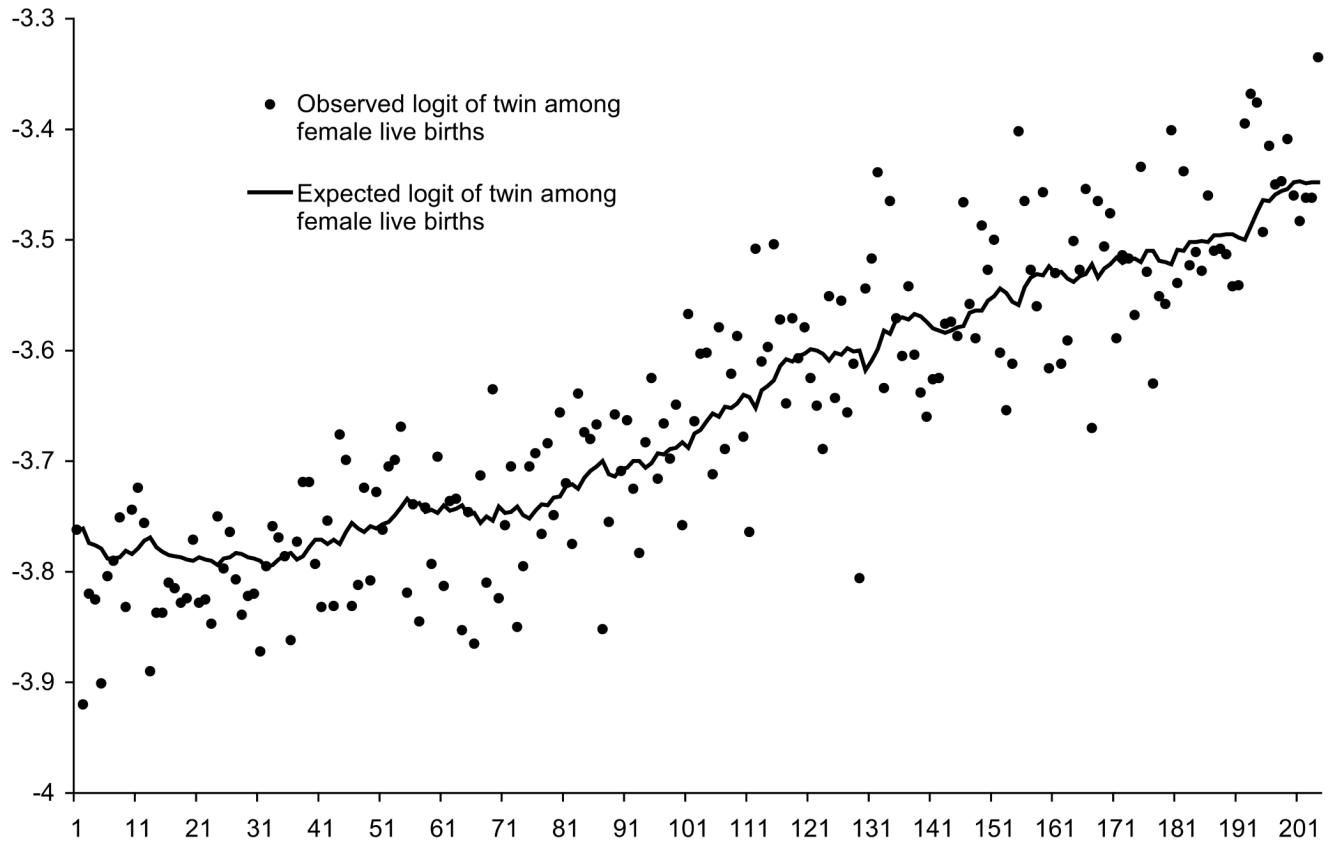
Figure 2.
Observed and expected logits of a twin among female live births in California for 204 months
beginning January, 1989 and ending December, 2005.

Figure 3.
Observed and expected logits of a twin among male live births in California for 204 months beginning January, 1989 and ending December, 2005.

Table 1

Best-fitting Box-Jenkins equations of the natural logarithm of monthly odds of a twin among 100 females or males born in California from 1989 through 2005. All parameters fall outside their 99% confidence intervals (2-tailed test).

	Equation
Females	
	$\nabla Z_{ft} = .0018 + (1 - .9070B)a_t$
Males	
	$\nabla Z_{ft} = .0019 + (1 - .9445B)a_t$

Table 2

Estimated coefficients for full and reduced equations in which the unexpected values of the monthly logit of a twin among male live births in California from 1989 through 2005 predict the unexpected values of the logit of a twin among female live births (standard errors in parentheses).

	Full Equation	Reduced Equation
Odds of twin among male births during		
Same month as odds of twin among female births	.3179[**] (.0681)	.3236[**] (.0677)
Month before odds of twin among female births	-.1353[*] (.0686)	-.1412[*] (.0682)
Two months before odds of twin among female births	-.1405[*] (.0681)	-.1522[*] (.0672)
Three months before odds of twin among female births	-.0665 (.0679)	

Moving Average Parameter

[*] p < .05; 2-tailed test

[**] p< .01; 2-tailed test