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Do Recurring Outbreaks of a Type of Infectious Immune Impairment Trigger Cyclic Changes in the Gender Ratio at Birth?

Rodney P. Jones

Healthcare Analysis & Forecasting, Honister Walk, Camberley, UK

ABSTRACT

Unexpected step-like increases in emergency medical hospital admissions, general practitioner (GP) referrals, and wider health care costs that appear to repeat at an interval between three to eight years in length have been observed in the United Kingdom (UK) and other countries. Based on the observation that the step changes appear to be restricted to a group of diagnoses associated with infection or inflammation, it has been proposed that outbreaks of an unknown type of infectious immune impairment are responsible for the cycle. Both infection and inflammation have been implicated in changes in the gender ratio (male-to-female births) observed in humans and animals, and this development presents an opportunity to test the infectious outbreak hypothesis. Monthly live births in England and Wales between 1980 and 2008 were studied. After adjusting for the effects of the solar sunspot cycle and season on the gender ratio, the pattern in the residual ratio (actual minus predicted) appears to align with the cycle of step changes in medical admissions and costs. It appears that each outbreak initiates a cascade of condition-specific effects, which include conception and/or fetal loss along with other effects on adults, and more specifically on the elderly. An additional peak in the gender ratio for conceptions in September, October, and November 1986 appears to correspond to the impact of fallout from the Chernobyl nuclear accident in April 1986 and seems to confirm the results of other studies on the impact of low levels of nuclear radiation on the gender ratio. *Biomed. Int.* 2013; 4: 26-39. ©2013 Biomedicine International, Inc.

Key words: Birth, gender-ratio, immunity, infection, inflammation, radiation

INTRODUCTION

The differential sensitivity of the male and female fetus to adverse intrauterine outcomes such as congenital anomalies, spontaneous abortion, and stillbirth have been well documented.[1-3] There is a primary relationship between the gender (male-to-female) ratio and sunlight, hence also latitude[4,5] and other factors such as war, exposure to particular types of pesticide and fungicide, racial origin, occupation and socio-economic status of the mother, age of the mother at conception, birth order, temperature, season, weather shocks, presence of a range of inflammatory medical conditions and infectious agents during pregnancy, and proximity to sources of nuclear radiation.[6-23] The most extreme example of the gender ratio appears to arise from the genetic condition causing familial primary pulmonary hypertension (FPPH), such that the usual gender ratio of around 1.06 is reduced to 0.76.[10] Central roles for inflammatory cytokines and hormones have been suggested to explain the response to such a wide range of physiological and psychological stressors.[9,19,20]

Address correspondence to Rodney P. Jones, PhD, Healthcare Analysis & Forecasting, Honister Walk, Camberley, GU15 1RQ. Phone: +44 (0)7890 640399. Email: hcaf_rod@yahoo.co.uk

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The time trends in the gender ratio are complex and appear to show long-term and short-term cycles.[17,22] A long-term cycle can be seen for births in Scotland from 1855 to 2007, in which there are two broad cycles with minima around 1903 and 1992.[24] There is an additional weak dependency on the approximately 11-year solar sunspot cycle.[4,5] Unexplained minimum and maximum values are observed in all countries, with the Cayman Islands having a minimum of 0.86 in 1994 and Macao having a maximum of 1.12 in 2000. The United States of America (USA) has distinct minima in 1972, 1991, and 2001[17,22], and there are unusual long-term oscillations in the gender ratio for births in Scotland conceived in the month of December.[25]

With respect to the role that infectious and inflammatory conditions may exert on the gender ratio, a potentially new type of immune function disorder has been recently proposed in an attempt to provide a rational framework with which to explain curious changes in both emergency medical admissions and associated health care costs, which appear to occur in a cycle that is three to eight years in length. The effects are specific to age and gender, are associated with diagnoses relating to infection and inflammation, and have been documented in the United Kingdom (UK), USA, Canada, and Australia.26-45 The commencement of each outbreak is accompanied by an increase in deaths, changes in the incidence of specific cancers[27,40-44], and an increase in occupation of hospital beds for particular medical conditions[29,38,39], and initiates a time cascade in the incidence of additional conditions.[46,47]

The discovery of a new type of immunological disease that leads to a higher incidence in infection and inflammation could offer considerable insight into the unexpected increase in prevalence of certain types of disease observed over the past 30 to 40 years.[38,48] Before accepting that such a disease exists, the proposed spectrum of effects must be tested in the widest possible context, and on this occasion a relationship with the gender ratio at birth would add additional support to the proposed hypothesis.

Of relevance to the potential effect upon the gender ratio is the observed propensity of the proposed disease to influence the health of women more than the health of men, and this effect appears to be stronger against older women.[34,37] The potentially deleterious effects of infection during pregnancy cannot be excluded given that pregnancy is effectively a state of immune impairment that involves the production of regulatory T cells that ameliorate autoimmunity[49], an increase in levels of interleukin-6, interleukin-8, and adhesion molecules, and the activation of leukocytes.[50] A recent study has demonstrated a specific increase in the costs associated with neonates following the most recent outbreak in England in 2007.[36] If the observed changes in admissions and costs are due to an immune impairment, then that immune impairment possibly could cause corresponding cyclical changes in the gender ratio by increasing infection and inflammation in the mother and the fetus, by eliciting an effect specifically against the female fetus, or by altering the forces that result in the usually higher loss of the male fetus.

An estimated 15% to 20% of pregnancies end in spontaneous abortion, and although 50% of miscarriages and 55% of stillbirths are attributed to chromosomal abnormalities,[51] this still leaves the cause of 7% to 10% of lost conceptions unexplained. Somewhat confusingly, reported gender ratios for miscarriage range from 0.71 to 1.3.[52,53] The lower of these two figures is for chromosomally normal miscarriages and thus suggests the possibility of higher female loss due to other reasons.

Most studies on the gender ratio use annual totals, and time series constructed on this basis show a series of peaks and troughs that can arise randomly or are due to environmental or infectious factors specific to particular months in any given year. Given that the timing and severity of such environmental or infectious factors can be highly variable, the application of simple annual totals would blur the contribution from such events. A monthly time series must be constructed to detect changes that might arise closer to the time of such outbreaks. This study uses a running 12-month total of residuals against an annual seasonal cycle to detect semi-permanent changes in the gender ratio. Results are presented for live births in England and Wales from 1980 to 2009 to investigate if outbreaks of a new type of immune impairment correspond to changes in total live births or to a characteristic time pattern in the gender ratio at birth.

MATERIALS AND METHODS

A record of monthly live births in England and Wales from January 1980 to December 2008 was obtained from the Office of National Statistics (ONS). The number of monthly births ranged from a minimum of[45,150] in February 2001 to a maximum of 62,490 in July 1990. To determine if there were particular changes in the total number of live births, the monthly births were divided by the number of days in each month to give births per day. The average was then calculated for each month.

In order to exclude the known effect of season on the gender ratio, the average gender ratio for each month was determined as the baseline position and monthly residuals against this baseline position were calculated. A monthly count of sunspots using the international sunspot number was obtained from the website of the National Oceanic and Atmospheric Administration (NOAA).[54] The minimum average daily count was 1 in October 2007, and the maximum average daily count was 200 in August 1990. The effect of the approximately 11-year sunspot cycle was determined by adding an increment to the raw monthly gender ratio. The value of the increment is equal to $A \times N + B \times N^2$, where A and B are constants and N is the average daily sunspot number per month. The proportionality constant was determined by minimizing the sum of the absolute difference between the adjusted actual values and the expected average monthly value seen over the 28-year period. The solver function in Microsoft Excel was used to minimize the sum of residuals by adjusting the values of the constants A and B. Values for the constants A and B were 1.11×10^{-6} and 1.24×10^{-9}, respectively. These values were confirmed by manually changing the values of the constants in order to observe the effect on the sum of the residuals. Dates for the initial outbreaks of the hypothesized immune impairment were obtained from earlier studies.[25-46]

RESULTS

The existence of a seasonal cycle in the gender ratio is well known.[4,5] Figure 1 presents the average gender ratio in England and Wales over a 19-year period. It is useful to observe that the seasonal cycle in the gender ratio observed in Figure 1 is consistent with that reported by others[4,5,8,11,13] and that the average gender ratio in England and Wales has remained relatively constant at around 1.052 over the past 28 years, as opposed to a gradual reduction in the USA from 1970 to 2002.[17] The appearance of a small peak around December, which corresponds to conception in March, in Figure 1 is consistent with the observation that the seasonal nature of the gender ratio depends on the mother's weight at the point of conception. Mothers weighing less than 62 kilograms (kg) have two seasonal

peaks, whereas mothers weighing more than 62 kg have only one peak.[55] The second peak, which is smaller, has also been observed to occur in the USA[4], and the incidences of various cancers, mental health problems, and other conditions have been observed to show a larger peak and a smaller peak.[56-58]

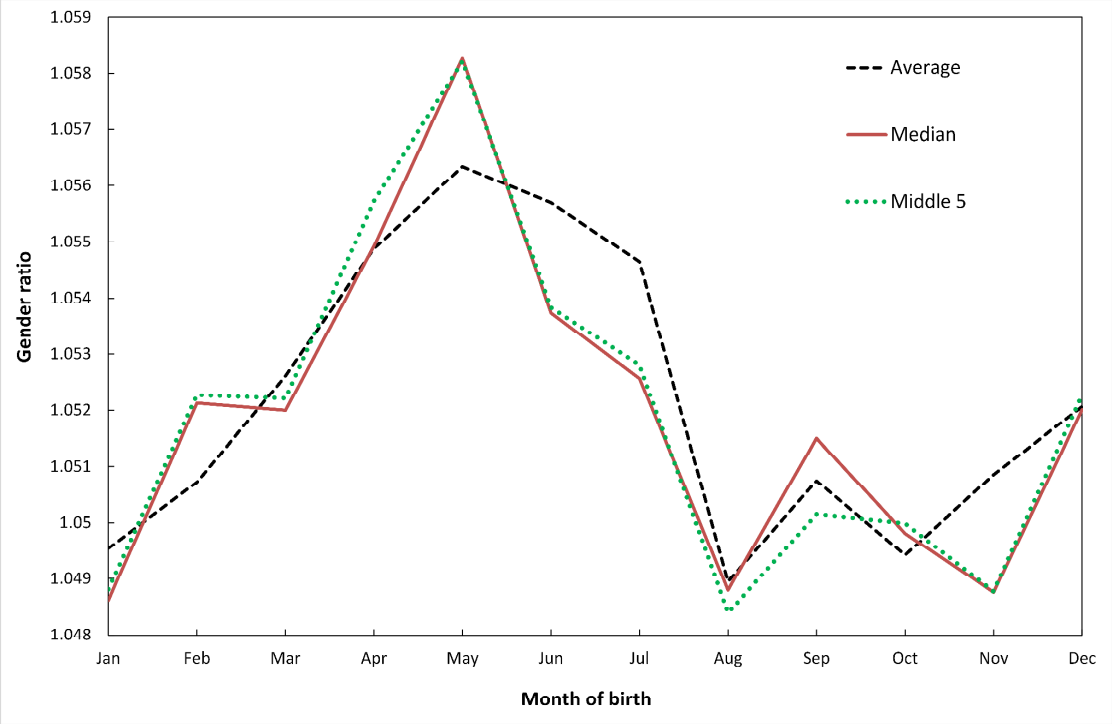

Figure 1: Seasonal cycle in the gender ratio for England and Wales. Average and median (middle of ranked values) monthly gender ratio is over the 29 year period. "Middle 5" is the average of the middle 5 of the 29 ranked values for each of the months.

The role of statistical randomness in detecting changes in the gender ratio requires comment.[59] The gender ratio, while sensitive to the environment, is still well maintained for fairly obvious biological reasons, so the author is looking to detect small differences. Simple randomness can generate variation around the average even with the large numbers of monthly births used in this study (45,000 to 63,000), and for this reason two estimates of the monthly average were included in Figure 1. The average is the usual numerical average over the 29 years, whereas the average of the middle five values uses the concept that the median can often provide a better estimate of the real average when the data series contains high or low values arising from external causes.[60] Figure 2 has been included to explore these issues and shows that a higher average is associated with a ranked series of gender ratios, which are consistently higher (May) than those obtained from a series associated with a lower average (January or August). Thus, the use of a 29-year time series allows sufficient discrimination between months of generally higher or lower gender ratios.

Figure 3 demonstrates that a seasonal cycle in the average number of births per day occurs each month. This seasonality has been shown to be largely related to the effects of heat and humidity, which will affect the frequency of intercourse.[61] The peak of births in September corresponds to conception in mid-winter, and the lower number of births from February to April corresponds to conception in the summer, but neither result explains the minimum number of births in December and January, which correspond to conception in

February and March. In this respect, vitamin D levels reach a seasonal minimum in February and March[62], and adequate levels of vitamin D appear to be involved in successful conception.[63] No direct link appears to exist between the gender ratio and relative number of births in each month.

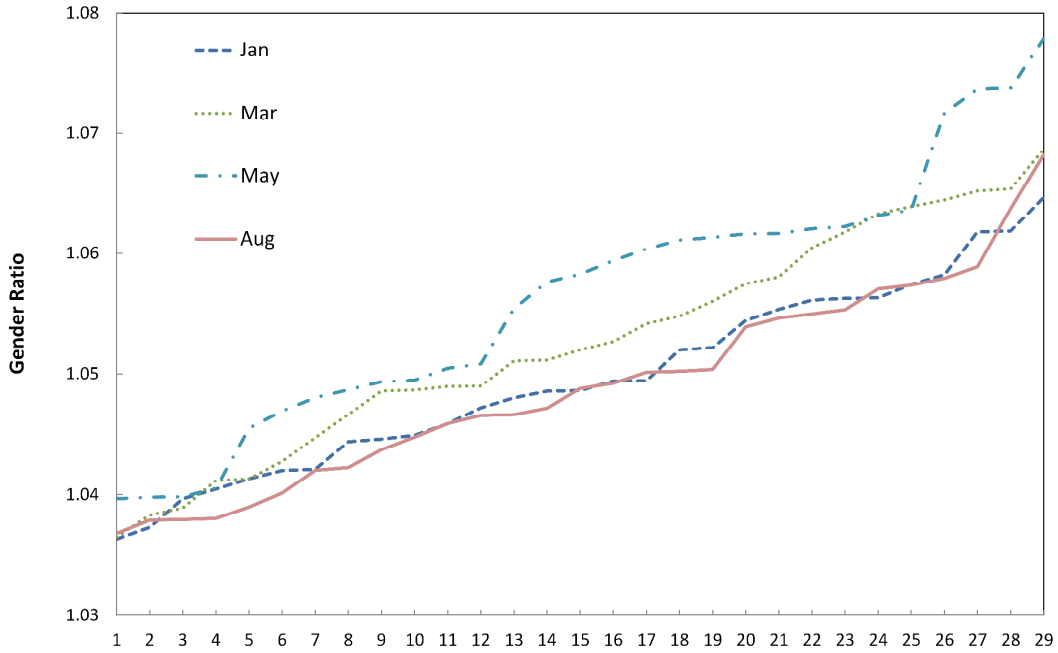

Figure 2: Ranked values for month of birth. Each line gives a ranked series of gender ratio for each month of the year over 29 years.

The role of the approximately 11-year solar sunspot cycle was investigated by calculating a gender ratio adjusting factor comprising a polynomial relationship with sunspot number, i.e., solar radiation intensity. This adjusting factor was added to the actual monthly gender ratio and the values of the constants were determined by minimizing the sum of the absolute residuals. The maximum effect of the sunspot cycle was only a +0.00027 (0.035%) change to the raw gender ratio observed at the monthly maximum of sunspot activity seen in August of 1990. The positive effect of sunspot number at conception (even though weak) is consistent with the higher gender ratio observed in summer, i.e., generally higher light intensity increases the gender ratio. The effect on gender ratio was dominated by the linear part of the equation rather than the part determined by sunspot number squared, and at highest sunspot numbers the linear part made a seven times higher contribution than the number squared contribution. This sensitivity of the gender ratio to the solar cycle is generally smaller than that observed in the USA[4] but this is consistent with the higher latitude of the UK compared to the USA. Hence, although there is an effect due to the solar cycle, its impact on the data for England and Wales is too small to influence the results, which are largely dominated by season as per *Figure* 1.

The trend in the residual gender ratio (after adjusting for season and sunspot number) for births occurring in 1980 to 2008 is given in Figure 4, along with the approximate dates for the onset of the outbreaks of the proposed new immune disease. Note that the date of onset is approximate as the full spread of this proposed disease across the whole of England and Wales appears to occur over a period of one to two years, although the bulk of this spread has occurred within the first year.[42,44-46] This progressive spread is the principal

reason that the residuals have been summed over a 12-month period. It would therefore seem that shifts in the average gender ratio calculated using a running twelve month total are associated with outbreaks of the proposed new disease. While a running 12-month total is useful it does need a degree of interpretation. Hence the peaks in *Figure* 4 are indicative of a period of higher gender ratio over the previous 12 months.

One possible way in which the gender ratio is modified could be via changes in total live births. The trends in live births in England and Wales are made up of a series of peaks and troughs emanating from the Second World War baby boom.[64] Additional undulations could arise from the interaction between the weather and births.[61] These complexities aside there appears to be a general linkage between onset of the outbreaks and subsequent spatiotemporal spread and a period of higher total births. This is illustrated in Figure 5 for the late 1992 outbreak. This outbreak was noted in Reading (south of England) to arrive at the end of the second week in March 1993 as part of its wider spread across the UK.[65] This event happened on the downward side of the 1990 peak in births, which eventually reached a minimum in 2001[64], hence the downward slope in *Figure* 5.

In *Figure* 4, a further peak in the gender ratio for conceptions in 1986 appears to correspond to the Chernobyl nuclear accident, which commenced on April 26, 1986. The gender ratio for conceptions in September, October and November of 1986 lay at the 98.3%, 97.1% and 93.4% confidence intervals respectively, i.e., three consecutive months above the 93% confidence interval with a probability of 3×10^{-5} for a three in a row occurrence. The 60 to 150 day lag between the start of Chernobyl and these peak months is consistent with the point at which radiation from ^{134}Cs and ^{137}Cs climbs to its highest level.[66] In the UK, curbs on the movement of animals from the worst affected farms were still operating some 20 year later[67], but the human food chain in the UK is complex with multinational flows of food from across Europe, so additional isotopes could have entered via this route.

DISCUSSION

Of relevance to this study is a curious reduction in emergency hospital medical admissions, which seems to occur around 3.5 years after the initial outbreak. Some form of collective switch of the infectious agent to a dormant state has been proposed to account for this behaviour.[33] This specific behavior could possibly account for the dramatic fall in the gender ratio that seems to occur prior to each outbreak other than the one in 1996, where the next outbreak occurred after only three years and hence precluded the proposed switch to a dormant state. Therefore, the removal of the infectious agent (via the proposed switch to a dormant state) appears to facilitate a switch to a higher ratio of female births and this is consistent with the evidence that the male fetus is, in general, more sensitive to infection and inflammation while in the womb. The behavior around the 1996 outbreak also appears consistent with a different pattern of infection, i.e., short interval, between 1993 and 1996.

Given the propensity of the cycle of events surrounding outbreaks of the immune impairment to cause an increase in the gender ratio at specific times (*Figure* 4) it is possible that additional fluctuations in the background seasonal trend seen in Figure 1 between November to May could be due to the presence of a number of the outbreaks over the 28-year period, i.e., the large peak arising from an outbreak during the period when the gender ratio is lowest (winter) will have a greater effect than against the higher summer ratio.

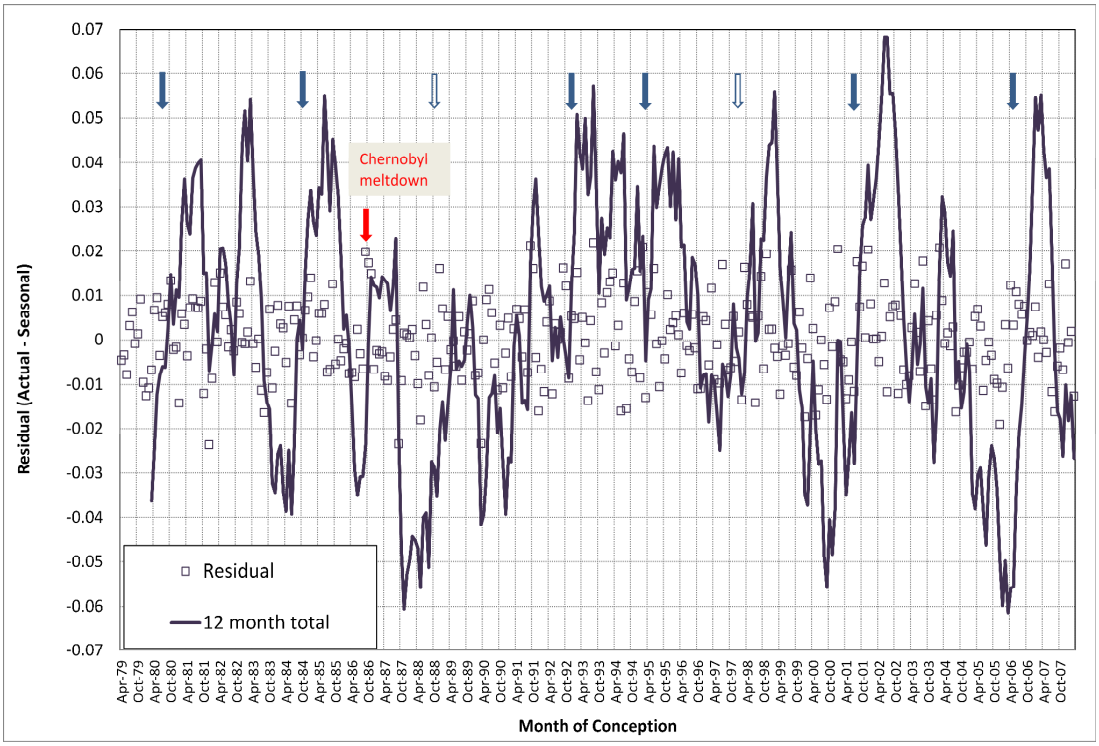

Figure 4: Trend in the gender ratio over time. Residual is the actual gender ratio (after adjusting for solar flare count) minus the expected average seasonal pattern in gender ratio. The 12-month total line gives the sum of the residuals using a running 12-month total. Arrows mark the approximate onset for the outbreaks of the proposed new immune disease. The X-axis gives the month of conception. The open arrows are for outbreaks that appear to be confined largely to Scotland (not included in this study) and parts of northern England (a subset of the data covering England and Wales).

Two smaller peaks in the gender ratio appear associated with the more limited 1990 and 1999 outbreaks, which appears only to have affected Scotland and parts of northern England.[28,68] On these occasions the peaks are smaller because the data do not include Scotland, i.e., there is a partial effect seen within the larger data set for England and Wales. Both of these outbreaks appear to relate to similar outbreaks observed in the USA somewhere around 1990 and 1998.[35] The positions of the first two arrows in Figure 3 have been estimated from historic changes in accident and emergency (A&E) department attendances for England[69] and also appear to correspond to slightly earlier outbreaks in the USA around 1979 and 1986.[35]

The data in *Figure* 4 have been adjusted to show month of conception (month of birth minus nine months). This may not represent the exact adjustment required to reflect the impact of this new disease most aptly since, in general, the greatest loss of developing fetus occurs in the 8th to 12th week of pregnancy.[3] Other studies suggest that the greatest incidence of Crohn's disease and schizophrenia occurs at month six of gestation, where the mother is exposed to measles and influenza respectively.[70-72] The exact point at which the fetus is most sensitive to this proposed immune impairment remains to be quantified by further study. The key point is that there is a cycle corresponding to known dates for outbreaks.

The potential linkage between outbreaks of the proposed agent and a temporary increase in live births requires additional research, which will need to disentangle the effects of the weather from the effects of the outbreak and probably needs to be conducted at regional rather than national level. Since a running 12-month total has been used in Figure 5 a step

increase in births will generate a ramp upward with the full extent of the step revealed 12 months later.[33] However, on this occasion, the step change is not permanent and hence the ramp is truncated eight months later. An estimate of the initial step increase is 5,830 additional births at an initial 670,740 births, i.e., a 0.9% increase. It has been proposed that the primary gender ratio may be as high as 1.7 giving the possibility that the additional births are all male.[73] If these births were all males this would be sufficient to shift the gender ratio from 1.052 to 1.070, which is in excess of the actual shift to around 1.056, i.e., the extra births are certainly enriched in males but not exclusively. Such a shift to higher male conceptions would then allow a high gender ratio to appear in those subsequently lost via spontaneous abortion. However, this possibility will require further study to resolve. Indeed like Chernobyl (see below), we may only be dealing with an effect lasting two or three months and possibly against fetuses at a specific age of development. Closer inspection of *Figure* 4 seems to indicate that this may be the case. Hence we are dealing with a very complex set of interactions with time cascades determining both live births and gender ratio.

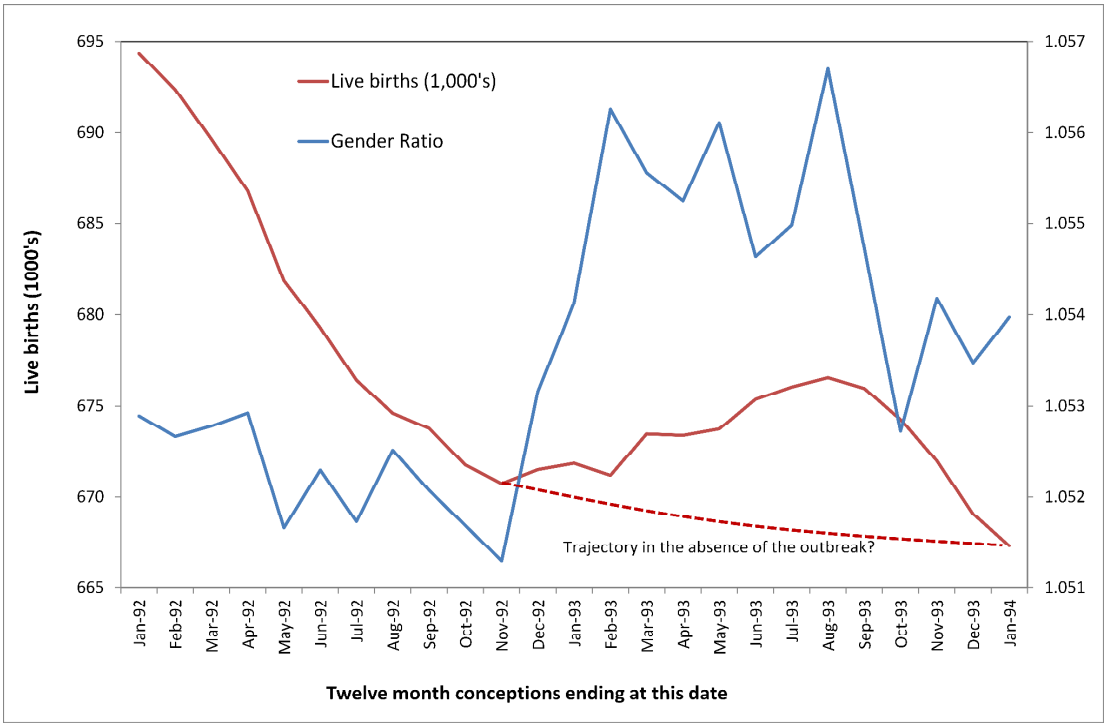

Figure 5: Change in live births.

The Chernobyl accident occurred during a period of generally rising births due to the successive waves in births emanating from the Second World War baby boom[64], but there is some evidence to suggest that, in opposition to the proposed outbreaks, the effect of low levels of radio-isotopes led to a small reduction in live births. After adjusting for the effect of season, conceptions leading to a live birth in 1986 for September, October and November were 1919, 1868 and 1852 per day respectively, i.e., a small temporary dip. This is not conclusive evidence; however, there is no evidence for an increase in births as seems to be associated with the proposed outbreaks. This curious increase in the gender ratio arising from exposure to low levels of nuclear radiation[23] could explain peaks in gender ratio in the USA around 1962 that correspond to peak levels of nuclear fallout from above-ground atomic bomb tests, while further peaks in the US in 1979 and 1986[17] appear to correspond to the Three Mile Island and Chernobyl meltdowns respectively. In this respect it is of in-

terest to note that in England an abnormal peak in the stillbirth gender ratio of 1.114 was observed to occur in 1963[3], which corresponds to the peak in fallout from above-ground atomic bomb tests.

It needs to be noted that high levels of nuclear radiation cause the opposite effect on the gender ratio, and in six eastern regions of the Czech Republic fetuses in the third month of development (onset of thyroid gland function) exposed to very high levels of ^{131}iodine led to a loss of around 400 male new-borns.[74,75] This effect was not observed elsewhere in the Czech Republic that were not exposed to immediate very high fallout.

However, the key observation is that the peaks and troughs consistently align with known dates for Chernobyl and the proposed outbreaks. At this point it is of interest that troughs in the gender ratio seen in the calendar year totals for the USA[17], i.e., the minimum prior to a switch to higher gender ratio seen in *Figure* 4, appear to correspond to the dates for the proposed outbreaks of this disease over a 40 year period.[35] Obviously these are not the only troughs seen over this period given the possible effect of multiple types of infectious outbreaks and other environmental factors; however, these findings suggest that reanalysis of data from other countries using monthly rather than annual totals may be useful to confirm this hypothesis.

The specific role of gender in immune function is a rapidly developing area[76] and the most enigmatic finding of this study relates to the apparent cycle in the gender ratio associated with the proposed outbreaks. In *Figure* 4, a peak in the running 12-month total represents a 12-month period where males are favored, while in a trough females are favored. The troughs (females) all appear to occur in the period when the switch to a dormant state has been proposed to occur.[33] Hence absence of the 'disease', with its proposed greater affinity to infect or cause disease in females, results in higher female births while an outbreak of the disease results in a peak in male births, i.e., selective loss of females rather than the usual selective loss of males that has been observed in the historical literature.[1,2] Indeed, exposure to low levels of nuclear radiation and preceding warm years and /or a preceding colder month are other examples of an environmental challenge that favors male gender at birth.[19,23,77]

Regarding radiation, it has been noted that the cells composing the immune system are among the most radiosensitive in the body.[78] Given that this new type of immune impairment has been proposed to emerge in the early 1960s[34] and that it only occurs at three to nine year intervals, it is possible that the historical gender ratio trends need to be reappraised against these new findings.

It has been proposed that the ubiquitous herpes virus cytomegalovirus (CMV) is the agent responsible for these outbreaks.[79] While the principal effect of each outbreak is against the elderly, a genuine infectious outbreak should affect all ages; however, the effect will be appropriate to the particular age of the person infected. CMV is well known for its role in adverse intrauterine outcomes such as stillbirth and (mainly neurological) congenital malformations.[80-83] CMV appears to exert its maximum effect if infection occurs in the first trimester.[80] Other bacterial, viral and parasitic agents are known to affect the gender ratio and cause adverse intrauterine outcomes[16,84,85] but none are capable of the wide range of immune evasive and modulating effects produced by CMV. While this study has not proved that CMV is the infectious agent it adds to the growing body of evidence pointing in that direction. In this respect data from Scotland suggest that each outbreak could also be associated with an increase in stillbirth.[68]

Limitations

Studies investigating the causes for changes in the gender ratio are made notoriously difficult owing to the role of statistical randomness. This study has sought to avoid this problem by using births across the whole of England and Wales. However, if the agent responsible for changes in the gender ratio is showing spatial spread over the space of around one year, then the effects upon gender ratio may be partly obscured. The use of a running 12-month total of the residuals could well be a crude way of attempting to extract the true underlying pattern seen at a smaller local level. This study is not claiming that the effect against gender ratio is particularly strong but there is enough to suggest that could be a plausible association. It should also be noted that not every peak and trough has been explained. Indeed, to achieve this would be unlikely owing to statistical randomness and a multitude of other infectious and environmental (notably temperature) effects capable of influencing the gender ratio.[77]

Interpreting other studies

The above observations raise questions regarding the interpretation of studies on adverse events in pregnancy, in that results from different time frames can give apparently conflicting answers. For example, a recent study on stillbirth in England was conducted over the period 2009 to 2011.[86] From Figure 3 we can see that this covers a period when the gender ratio has reverted back to more 'normal' behavior and hence a gender ratio of 1.2 in the stillborn confirms previous observations that the male fetus is generally more sensitive to loss during pregnancy. It would seem that we need a set of studies that specifically cover the short period of time surrounding each outbreak when active infection of the causative agent is apparently creating a unique situation.

CONCLUSIONS

The gender ratio at birth in England and Wales appears to show a pattern consistent with the timing of proposed outbreaks of an infectious immune impairment. The novel feature of these outbreaks is a temporary increase in the proportion of male births. This is a unique finding against a generally higher sensitivity of the male fetus to infection and inflammation and hence to a reduction in the gender ratio at birth. However, the observation is consistent with the more pronounced effects of outbreaks of this 'disease' against females.

The evidence for this new immune disease appears to be mounting and urgent international research is required both to confirm and build upon the conclusions reached in this and previous studies. The logical extension of this work is to investigate the possibility of a linkage with congenital defects and other congenital problems[9,56,70-73], which seem to be implied by an increase in the cost of neonatal care following the 2007 outbreak in England.[36] Higher costs would naturally arise given the higher proportion of male births, who may also be infected but survive and thereby increase costs. Given that CMV is a psychotropic agent,[87,88] a further extension of this work would be to search for a matching cycle in the incidence and severity of postnatal depression.

In isolation, this study would merely be evidence for curious cyclic behavior in the gender ratio. However, when nested with the other more dramatic increases in GP referral, medical admissions and deaths, we now have a growing body of evidence pointing to a common infectious source and a possible candidate.

The next step in this research would be to repeat the analysis at regional level across the whole of the UK alongside data for deaths, medical admissions and GP referrals. Weekly analysis may be a possibility. In this respect, accurate data on hospital admissions will be available from around 2000 onward. Analysis at smaller geographies than regional level might not be feasible owing to the higher background noise from Poisson randomness; however, using the far higher sensitivity of medical admissions to these outbreaks should allow smaller geographical areas to be aligned regarding the point of onset and therefore summed to give a clearer picture of the effect against gender ratio.

Given the complexity in the trends it is also suggested that more sophisticated mathematical methods such as Fourier transforms or wavelet analysis be employed to understand possible patterns and sub-patterns further within the wider issues around changes in the gender ratio over time.

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CONFLICT OF INTEREST

The author provides consultancy to health care organizations.

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