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DEBATES

Further concepts on regulators of the sex ratio in human offspring

Non-optimal maturation of oocytes and the sex ratio

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Introduction

In a prospective analysis on women who had discontinued contraception to start pregnancy, Weinberg *et al.* (1995) uncovered new data on the notion of why some conceptions result in boys, while others result in girls. The length of the follicular phase (from the onset of the menses to ovulation) was found to be related to the sex of the baby in 133 pregnancies that survived to delivery: a short follicular phase tended to produce boys, while a long phase tended to produce girls. These results were not in line with those presented by others, particularly not with those on an orthodox Jewish population (Harlap, 1979) and with the U-shaped regression of producing a male *vis-à-vis* ovulation: the relative risk of a male conception is lower in the middle of the fertile interval, in contrast with at the beginning and end, as proposed by Guerrero (1974).

The results of a study on the sex ratios among polygamous and monogamous marriages (0.47 versus 0.53 respectively) in each of seven ethnic groups in Kenya (Whiting, 1993) do not correspond totally with this evidence. Female conceptions in polygamous relations would be increased if the decision about the timing of intercourse was determined by the woman and was therefore influenced by the (maximum) strength of her sexual desire at the time of ovulation. In monogamous marriages, the timing of intercourse would be determined by the husband, independent of the fertile days and would heighten the probability of producing a son. The relationship of male conceptions with ovulation is also substantiated by the consistent excess of female births after conceptions during the most fertile days and male ones after failure of the rhythm method (Shiono *et al.*, 1982; Gray, 1991).

The study by Weinberg *et al.* (1995) was well-designed, although the women enrolled were highly motivated to comply with the protocol of daily control and therefore highly selected. In addition, we were not informed about either the kind of contraception used, or the waiting time to conception after discontinuation. After stopping the pill, the follicular phase is known to be prolonged in the first (and subsequent) menstrual cycles (Larsson-Cohn, 1969; Homesley and Goss, 1970). Shiono *et al.* (1982) found a small excess of male conceptions in women who conceived within 2 months, while Rothman and Liess (1976) did not. The relatively high twin rate (six pairs of same-sex twins) in this population is remarkable and is also a reason for caution. Higher rates of twins have been related to cessation of oral contraceptives (Rothman, 1977; Métneki and Czeizel, 1980; Allen, 1981) and higher rates of monozygotic twins have been related to delayed ovulation (Bomsel-Helmreich and Papiernik-Berkhauer, 1976). For all these reasons, it can be questioned whether the results reported by Weinberg *et al.* (1995) apply to a 'naturally conceiving population'.

James (1995) compared the results of Weinberg *et al.* (1995) to the more traditional concept. To him, it seemed unlikely that both hypotheses could be true independently; direct and indirect evidence in animals and humans would favour the latter. In addition, he assumed a causal connection between a high coital rate and a high male sex ratio, which would not cohere with dependence on the length of the follicular phase. His concept is based on, among others, the well-established male excess during and just after wars and a decrease across the first year of marriage. A causal relation to higher coital rates during the first year of marriage and during or after wars (in which the home leaves of soldiers are not accommodated to their wife's mid-cycle), should be questioned. As stress has been found to affect the gonadotrophin secretion (Rivier and Rivest, 1991), these high male sex ratios can be connected with the emotional state of these women and with the inherent reproductive hormone imbalance and thus, more inappropriate maturation of the oocyte. This possibility is supported by the high male sex ratios found about 4 months before the wedding date (pregnant brides) and, again coinciding with this date, ratios that are higher than during the first year of marriage (Renkonen, 1970; Mattila, 1980). Before the contraceptive era, social stress was inherent to illegitimate rapports. These high male sex ratios also contradict the other claim of James (1990), that high levels of parental gonadotrophins would favour the production of females.

Relationship between a prolonged follicular phase and reproductive casualties

Returning to the data reported by Weinberg *et al.* (1995) even if they reflect the fact that more girls are born after a long follicular phase, there is still a large body of direct and indirect evidence of a relation between less optimum conceptions due to a prolonged follicular phase and a short luteal phase.

Inadequacy of the corpus luteum and short luteal span apparently have their basis in defective follicular maturation and subnormal secretion of both oestradiol and progesterone (Sherman and Korenman, 1974). These disturbances are related to specific transitional stages in the ovulatory pattern (Lenton *et al.*, 1984) and are characterized by a long follicular phase and non-optimum maturation of the oocyte, i.e. preovulatory overripeness ovopathy (PrOO).

This concept, due to a prolonged follicular phase or delayed ovulation, is based on the detrimental consequences of PrOO on blastocysts, zygotes and fetuses in animal experiments (Butcher *et al.*, 1975) and on the circumstantial evidence for this phenomenon in humans (Jongbloet, 1986). For example, a prolonged follicular phase and PrOO are suggested by a 'stepwise midcycle temperature rise' and a longer than normal hypothermic (or follicular) phase in the conception cycle of spontaneous abortions (Cohen *et al.*, 1976) and malformed infants (Troya *et al.*, 1985; Spira *et al.*, 1985).

Recently, this concept has been widened by advancing the resumption of meiosis using a small amount of luteinizing hormone (LH) and/or follicle stimulating hormone (FSH) and dissociation of ovulation in rat oocytes. This produced the same detrimental effects as those seen before and after implantation (Mattheij *et al.*, 1994). These new experiments may perhaps throw new light on our understanding of pregnancy loss (and high male sex ratios?) after a too-short follicular phase, as are usual in the U-shaped regression of pathological progeny and high male sex ratios.

In the literature on ageing oocytes, a change in the sex ratio favouring the male at conception or at birth has often been suggested, but explorative data after a physiologically or experimentally prolonged (or shortened) follicular phase in animals are still lacking. A high male sex ratio (145) was found in the progeny of diabetic mothers (Naeye, 1972), in whom the reproductive hormones are known to be compromised. In this paper, we argue that high male sex ratios are connected with transitional stages of the ovulatory pattern, characterized by a long follicular phase.

The vexing question in relation to the primary sex ratio at conception and fetal loss cannot be solved as long we are ignorant of the male–female ratio of the large number of preimplantation and the very early postimplantation losses. There is strong evidence, however, that differentially high male mortality *in utero* occurs in mammals (Meyers, 1978). The current opinion in humans is that contrary to many other claims, a male excess at conception is steadily depleted by preferential attrition of male conceptuses in the course of gestation and in the first week of life (Kline *et al.*, 1989). At the end of the first trimester of pregnancy there are probably ~120 male fetuses for every 100 females (Hytten, 1982). From that point onwards, male mortality always outstrips the loss of females. Excess male representation in late abortions and stillbirths reduces the sex ratio at birth to about 105 to 107 males for every 100 females in most European populations, but at birth, the boys tend to be thinner and biologically less mature (Purcell, 1995). If not stillborn, a larger proportion have congenital malformations (136), hyaline membrane disease (171), pulmonary haemorrhage (155), subarachnoid, subependymal, intraventricular and subdural haemorrhage (129, 150, 154 and 167 respectively), erythroblastosis fetalis (148), toxaemia (181), prenatal and postnatal infection (115 and 185 respectively; Naeye, 1972). This male disadvantage continues by excesses in the sudden infant death syndrome and by diseases acquired in childhood, such as meningitis, encephalitis and infections of the respiratory and digestive tracts (Winter, 1972). Affected males also outnumber females in dyslexia, infantile autism, stuttering and all diseases of language, i.e. the dominant hemisphere functions (James, 1992). Male losses in childhood reduce the ratio to about 100, where it remains between the age of about 20–50 years. However, males continue to decrease by more cases of suicide, cancer and heart diseases (Purcell, 1995). Beyond middle age, male mortality exceeds that of women, so that by old age, only 20 to 30 men remain for every 100 women (Hytten, 1982).

It is attractive to suppose that this disproportional loss of the less robust male may be accelerated *in utero*, e.g. in the case of extensive developmental defects. The low male sex ratio will have already been reached at birth instead of in adulthood, as is usual. This is presumably the case in neural tube defects according to the site and extent of the lesion (Bell and Gosden, 1978; Seller, 1986; Byrne and Warburton, 1987). It also explains some exceptions to the rule of high male sex ratios at birth. The same accounts for conditions of highly compromised maturation of the oocyte, e.g. at the very extremes of reproductive age, in maternal diseases, low standard of public health, etc. On this basis, it might be expected that deprived populations would show a low male sex ratio, while a relative increase would result from improvement in maternal health and maternity care, as has happened in Chile and England and Wales (Cruz-Coke, 1978).

Below we argue that a trio of reproductive phenomena: (i) high male sex ratios; (ii) more reproductive casualties; and (iii) relative fragility of the male fetus or individual leading to differential loss, can be connected with a long follicular phase. We restrict ourselves to three transitional stages in the ovulatory pattern, i.e. (i) short interpregnancy intervals, (ii) young and advanced maternal age and (iii) specific seasons.

Sex ratio and short interpregnancy interval

After abortion, parturition or lactation, i.e. after periods of ovarian inactivity, the coordinated hypothalamic and pituitary cyclic functions necessary for ovulation are resumed. The ovulatory pattern in this transitional stage varies considerably and has often been referred to as a 'second menarche'. In the absence of lactation, the ovulatory activity returns rapidly; in the case of lactation, the ovaries still remain relatively inactive or show low cyclic activity which gradually increases until menstruation is promoted. In either case, the initial ovarian activity may not be ovulatory and the follicular phase will tend to be longer than normal and the luteal phase shorter: delayed ovulation and inappropriate maturation (PrOO) are usual in these women (Jongbloet, 1986).

Following the hypothesis of Weinberg *et al.* (1995), an excess of girls would be expected in the case of short interpregnancy intervals. The reverse, however, was found in a study on 116 458 completed mormon sibships 'including all live births and some fetal deaths' (Greenberg and White, 1967): when sibship and birth rank were simultaneously controlled, the birth intervals before the male neonates were short, while those before the female neonates were long. A claim that the difference was due to immunization of the mother was rejected on statistical grounds (James, 1975). According to our concept, it is not the gender of the preceding child that determines the sex of the subsequent one, but rather the gradient of maturation of the oocyte in the conception cycle.

The teratogenic effect of very short interpregnancy intervals on fetal, neonatal, infant and childhood mortality and on developmental defects, but also on reduced height and ponderal development and psychomotor functions, have been stressed at other locations (Jongbloet, 1986). The high male sex ratios or the differential attrition of male fetuses or individuals in most of these casualties, have already been emphasized.

Sex ratio at the extremes of maternal reproductive age

It has been shown that the menstrual cycle is disturbed at both extremes of maternal reproductive age. In particular the luteal phase is short, which is negatively correlated with the length of the follicular or preovulatory phases (Lenton and Landgren, 1984).

Following the concept of Weinberg *et al.* (1995), an excess of girls should be expected in very young and older mothers. In contrast, Rostron and James (1977) and James (1987) concluded that when very large samples are analysed, the male sex ratio appears to decline with maternal age, irrespective of the birth order and paternal age. High male sex ratios have been found among women >50 years of age in England and Wales, Japan and the USA, which is too consistent to be dismissed (Hytten and Leitch, 1971).

It is extremely difficult to analyse the maternal age-related changes in the sex ratio, survival rate and differential attrition of the male fetus in the context of the follicular phase length. The results may be modulated and obfuscated by a precocious conversion of a high male sex ratio at birth due to disproportional attrition of the male conceptuses. This might particularly be expected to occur at the extremes of reproductive age, where the maturation of the oocyte is threatened the most (see Introduction). In addition, many factors are directly or indirectly involved in the maturation of gametes at conception: (inter)pregnancy intervals (that are longer at very young and advanced maternal age, shorter during middle age); constitutional diseases (lower prevalence of diabetes mellitus and thyroid disease at a young age, higher prevalence at older age); birth order (first and high order conceptions that are more frequently unplanned or earlier than really wanted; socioeconomic status (more unplanned conceptions at the extremes of reproductive age); duration of marriage and paternal age (involving delayed fertilization and sperm quality). Eventually, in the future, the continual changes in public health and education regarding reproduction and better contraceptive methods will continue to affect the results, just as in the past, as has been presumed in Chile and England and Wales (Cruz-Coke, 1978).

A maternal age-related excess of male stillbirths was much more pronounced at the beginning and at the end of reproductive life in the data presented by Cann and Cavalli-Sforza (1968). The only exception at one extreme (> 46 years) may possibly be due to precocious conversion to lower male sex ratios by disproportional loss *in utero*.

Sex ratio at birth and seasonality

A growing amount of data is being collected on seasonal fluctuations in the human ovulatory rate, on analogy with the heat periods in other mammals (Jongbloet, 1990; Stolwijk *et al.*, 1996). This seasonality in reproduction appears to be ruled by an endogenous rhythm, which is monitored by exogenous factors, such as photoperiodicity, temperature and energy balance. This implies transitional stages between 'anovulatory' and 'ovulatory' seasons with again inappropriate maturation of the oocytes, reflected by a long follicular phase. These are comparable with the transitions after menarche, before menopause and after pregnancy/lactation.

Again, following the concept of Weinberg *et al.* (1995), a higher birth rate of girls is expected during the seasonal transitional stages, i.e. before and after the birth optima, but not at the very peaks. In reality, the contrary is apparent. An analysis of the seasonal variation in both the sex ratio and the total number of births among about 52×10^6 births in seven different countries (around the turn of the century) stressed the seasonal coincidence in the increase in the number of female births (an 'inverted' sex ratio) and in the total births (Huntington, 1938). An analogous seasonal concurrence of female and total birth increases had already been recognized by Wolda in cattle and pigs, in agreement with that found earlier in humans (1927, 1929, 1935). Wolda concluded that the excess of male births is concentrated at the beginning and the end of the birth optimum, while female births coincide with the zenith of it. These naturally occurring variations in the sex ratio at birth were confirmed in two seal species and appear to be a general phenomenon: females pupping early in the season produced a male:female of ratio of >120:100, those pupping later on produced a complementary ratio of <80:100 (see Trivers and Willard, 1973). Wolda also suggested that the birth optima in humans coincide with the normalization of the menstrual cycles in the spring season.

Looking at the months at the major birth peak and neglecting the variations around the minor one, as did Huntington, this concurrence of higher female birth frequency with the major total birth peak is also apparent in The Netherlands, 1902–1928 (4 708 304 births, available years from CBS, The Hague; Figure 1), Germany, 1946–1967 (19 049 818 births, Gilbert and Danker, 1981; Figure 2) and Quebec, 17th and 18th centuries (157 155 births, Nonaka *et al.*, 1991; Figure 3). The same configuration was also present in the USA data (Slatis, 1953; Lyster, 1971; Janerich, 1971) where the major birth peak was 6 months removed; this is also the case in Australia in the Southern Hemisphere, 1911–1962 (1 907 818 births, Lyster and Bishop, 1965; Figure 4).

The configuration of the coincidence of higher frequencies of female and total births at the zenith of the birth optima, also appears to be modulated by social factors, such as the clustering of first births (Figure 5a) due to wedding dates in particular months (see Stolwijk *et al.*, 1996) and the hectic rise and fall of male births related to prenuptial and nuptial conceptions (see Introduction; Renkonen, 1970; Mattila, 1980). This becomes evident after separation of the non-first births (Figure 5b).

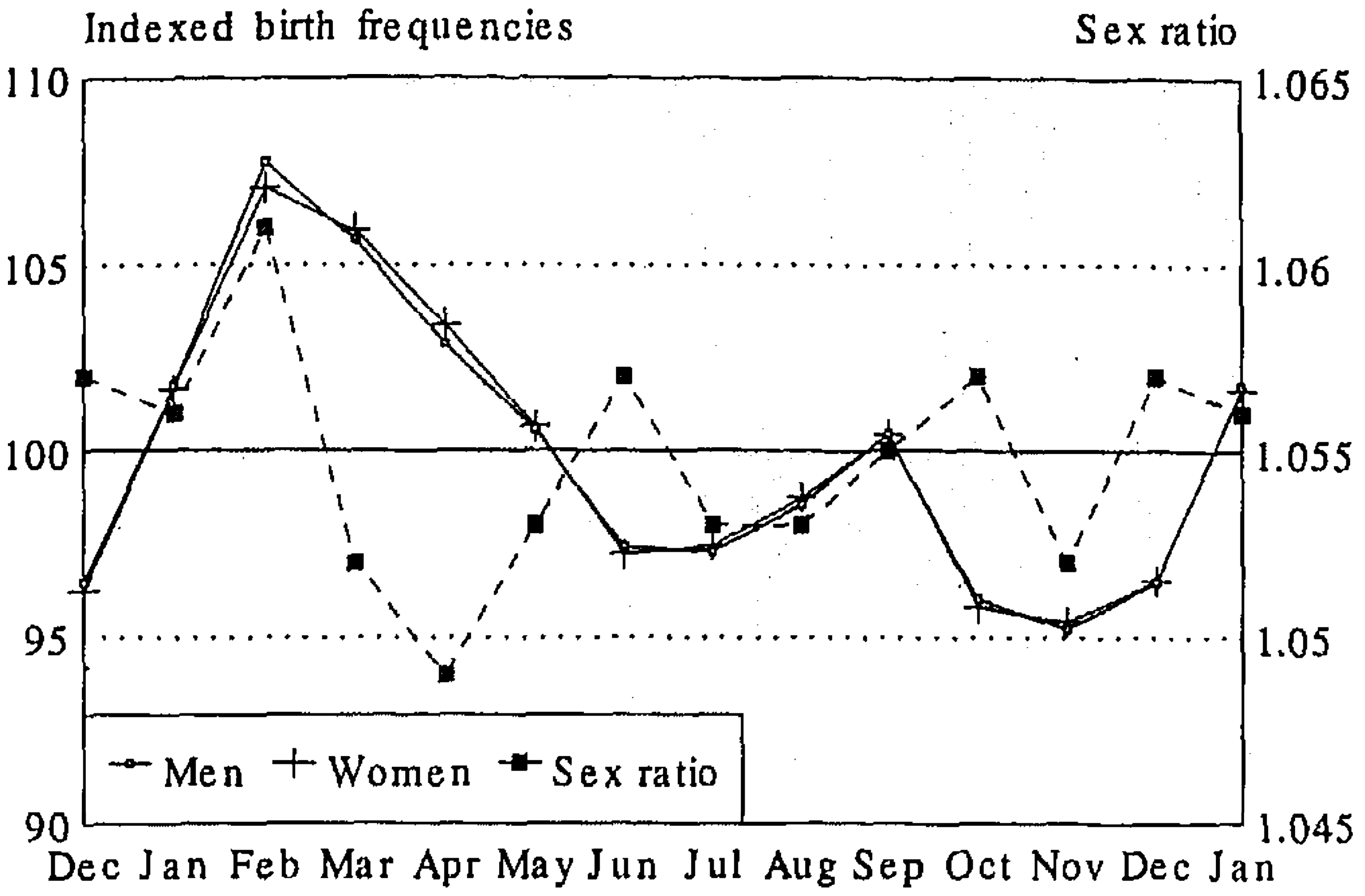

Figure 1. Indexed birth frequencies per month of male and female births in solid lines compared to the sex ratios in interrupted lines (The Netherlands, 1902–1928, n = 4 708 304 births; National Bureau of Statistics, The Hague).

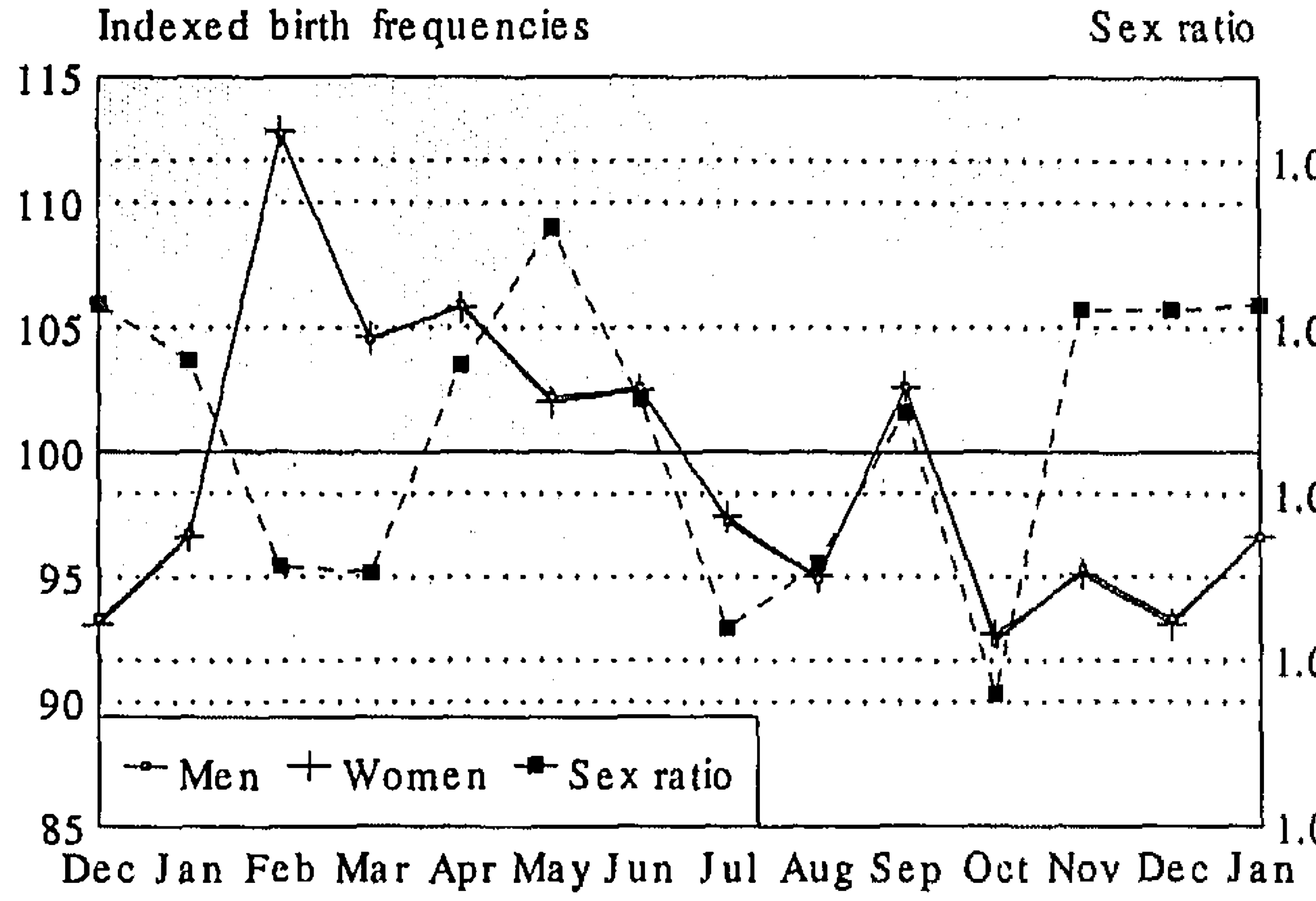

Figure 2. Indexed birth frequencies per month of male and female births in solid lines compared with the sex ratios in interrupted lines (Germany, 1946–1967, n = 19 049 818 births; Gilbert and Danker, 1981).

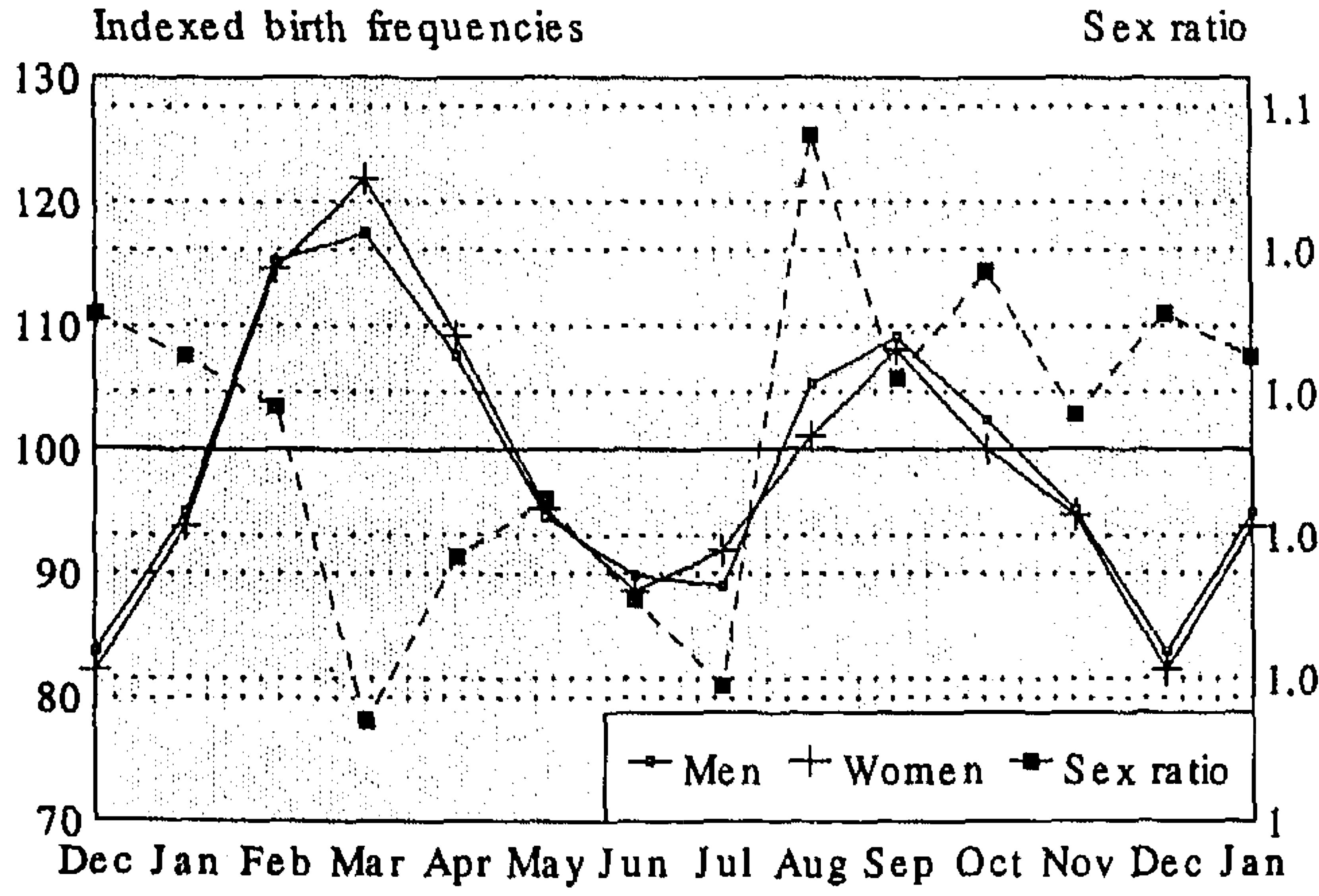

Figure 3. Indexed birth frequencies per month of male (80 566) and female (76 589) births in solid lines compared with the sex ratios in interrupted lines (Quebec, 17th and 18th centuries, n = 157 155 births; Nonaka *et al.*, 1991)

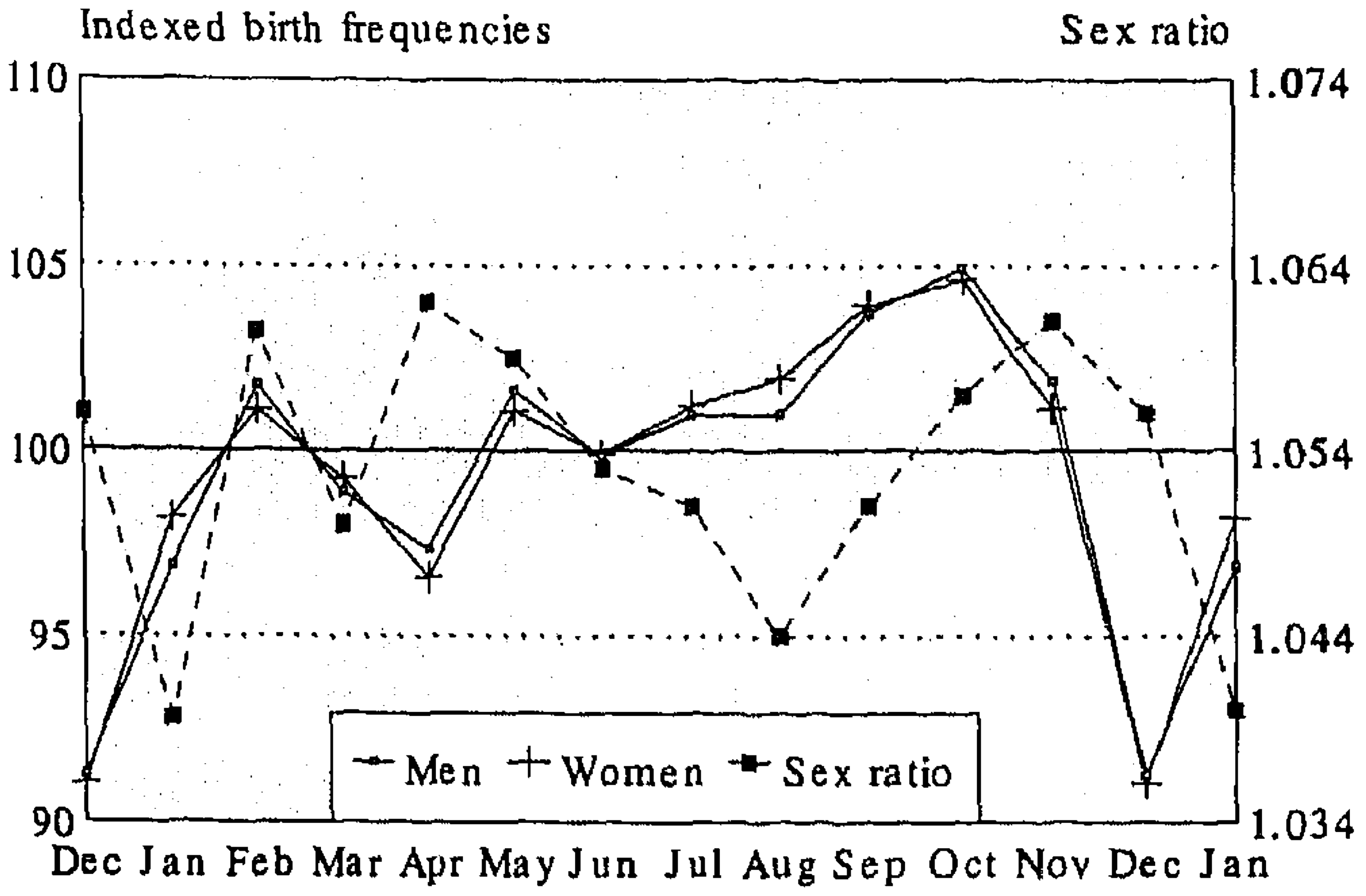

Figure 4. Indexed birth frequencies per month of male and female births in solid lines compared with the sex ratios in interrupted lines (Australia, 1911–1962, n = 1 907 818 births; Lyster and Bishop, 1965).

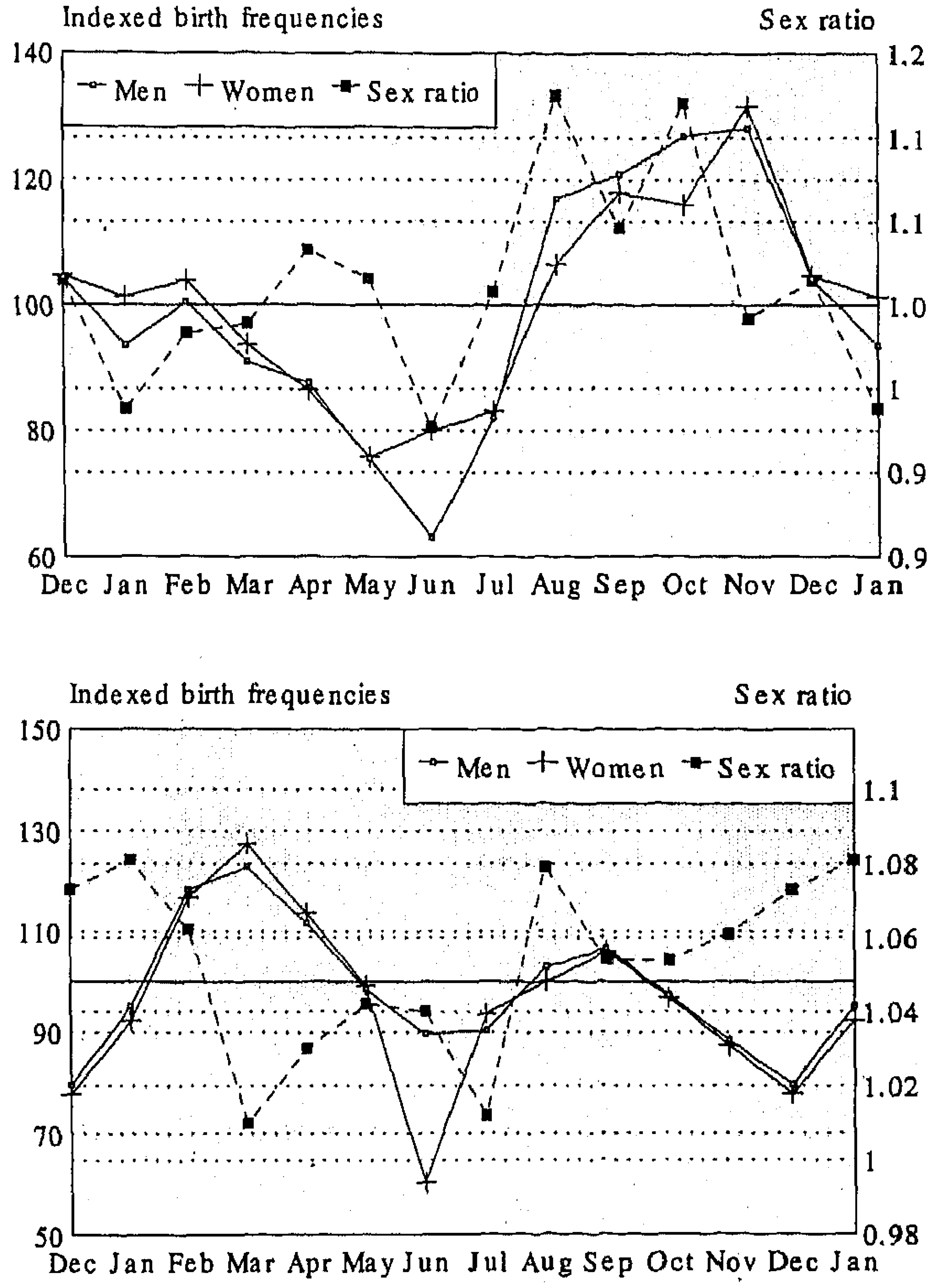

Figure 5. (**a**) as Figure 3 firstborns: n = 26 143; (**b**) as Figure 3 non-firstborns: n = 130 912.

Unaware of the earlier authors, James (1980) concluded that there can be no reasonable doubt about the existence of seasonal variation in the sex ratio at birth. In addition, there was synchrony with that of dizygotic twinning rates (in England and Wales) and of boys with undescended testes (in Hungary). This basic animal rhythm forms the basis of the seasonal preovulatory overripeness ovopathy (or SPrOO) hypothesis (Jongbloet, 1975; 1990; 1992) which explains the 'winter' birth excesses of stillbirths, neonatal deaths and many constitutional diseases, such as diabetes mellitus (Jongbloet *et al.*, 1988), schizophrenia (Pallast *et al.*, 1994), menstrual disturbances

(Jongbloet *et al.*, 1994) and non-familial Alzheimer's disease (Philpot *et al.*, 1989). The same basic animal rhythm was also used to formulate the seasonal optimum ripened oocyte (or SOptRO) hypothesis, which explains longevity in men and women (85 years old), when born at the zenith of the birth peaks (Jongbloet, 1992). Optimum maturation thus appears to go hand in hand with an optimum constitution in males and females and excess of female conceptions.

Again, in the total number of casualties (with the exception of sex-limited diseases) the male gender exceeds by differential attrition of male conceptuses and/or individuals. In stillbirths this disproportional attrition of males was also found to be present during specific seasons (Wolda, 1929).

The ability of nature to adjust the sex ratio in populations under food stress is a matter of great concern in biological and evolutionary thinking. It has led to several competing hypotheses, in which differential attrition of the heterogametic zygote (the male in mammals) plays the pivotal role (Trivers and Willard, 1973; Meyers, 1978). The combination of the physiological ability to adapt the phase and amplitude of seasonal reproduction according to the food supply and varying ecological conditions would enable animals and humans to modulate the sex ratio and the quality of the progeny. These 'acclimatization' and 'declimatization' principles were already formulated by Wolda (1927; 1929; 1935).

Conclusions

The high male sex ratio that occurs during the transitional stages of the ovulatory pattern, where a long follicular phase and nonoptimum maturation of the oocyte prevail, are in line with the traditional concept of a U-shaped regression of producing a male. They are, however, hard to reconcile with the findings of Weinberg *et al.* (1995) that a long follicular phase enhances a low male sex ratio (unless these cycles represent normal, physiological maturation of the oocyte).

The association of a trio of reproductive phenomena, i.e. high male sex ratio, less than optimum quality of the zygote and differential attrition of male conceptuses/individuals, fits better with the preovulatory overripeness ovopathy (PrOO) concept.

The trio of reproductive phenomena can also be expected in other conditions, characterized by non-optimum maturation of the oocyte and a prolonged follicular phase, e.g. subfecundity, endocrinological disease, stress situations, under-nutrition, over-excercise, etc.

Differential attrition of male conceptions *in utero* and the possibility of converting the sex ratio earlier than in adulthood as normally happens, implicates spurious interpretation of the sex ratios at birth in some casualties or in some conditions.

Differential attrition of male conceptuses/individuals in mammals combined with the ability to modulate seasonal reproduction according to the food supply and varying ecological conditions, implies a mechanism for sex ratio adjustment.

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Interpregnancy intervals, high maternal age and seasonal effects on the human sex ratio

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The appearance of a new hypothesis on sex ratio determination (that of Weinberg *et al.*, 1995) has predictably caused all the old hypothesizers (including me) to bark discordantly at it. However I should like now to divert attention to the contribution of Jongbloet *et al.* (1995). These authors are anxious about whether Wilcox *et al.* can reconcile their hypothesis with three findings which Jongbloet claims have a firm epidemiological basis. I suggest that none of these findings can withstand scrutiny. I shall treat them in order.

Sex ratio and short interpregnancy interval

Greenberg and White (1967) reported that short interpregnancy intervals are associated with male births. From this, Jongbloet *et al.* (1995) infer that short intervals between birth and conception are associated with male births. The inference may be correct, but interpregnancy intervals comprise two components: birth to conception (conception wait) and conception to birth (duration of gestation). It is not clear whether the explanation of these data may lie in the first component or the second. It is known that short gestations are associated with male births (James, 1994). It seems that Jongbloet *et al.*'s point fails if the association of sex with interpregnancy interval is secondary to an association of both with duration of gestation. It should be noted that short first birth intervals (i.e. from marriage to birth) are also associated with male births (Renkonen, 1970), yet those conceptions presumably occurred under none of the undesirable conditions proposed by Jongbloet.

Sex ratio and high maternal age

Jongbloet *et al.* (1995) cite Hytten and Leitch (1971) to substantiate the sentence that 'high male sex ratios have been found among women of >50 years of age in England and Wales, Japan and the USA which is too consistent to be dismissed'. As Jongbloet *et al.* (1995) acknowledge, large samples of data in England and Wales show a decline (not a rise) in sex ratio of births at high maternal ages (James 1972; James and Rostron, 1985). In regard to the Japanese data, Takahashi (1954) was undecided whether it was due to false registration of illegitimate children, especially male ones, by their grandmothers. This suggestion is supported by a number of lines of evidence concerning the reported sex ratio of Japanese twins (James, 1983). Lastly, as far as I know, the Takahashi effect has not been demonstrated at a conventional level of statistical significance in US data.

The variation of sex ratio with season

After reviewing this point, I concluded that there is evidence for seasonality in only one country, the US (James, 1987).