Gonadotrophin and the human secondary sex ratio

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Summary and conclusions

A review of published reports showed that the sex ratio (proportion of boys) was low among infants conceived after ovulation had been induced. The difference between the observed sex ratio and an expected one of 0.514 was highly significant. These findings suggest that maternal gonadotrophin concentrations at the time of conception directly affect the sex of the zygote.

Introduction

Evidence for the suggestion that the sex ratio of infants varies with the time during the fertile period that insemination occurs appears to be strong.¹ Direct data suggest that infants conceived early and late in the fertile period are predominantly male,

Index Medicus since the preparation of Wyshak's paper, and (b) scanning the *Science Citation Index* for references to the paper by Hack *et al*,⁵ which referred to the sex of infants of such pregnancies. The resulting list of papers, though doubtless not complete, seemed representative: this seemed to be so at least for the sex ratios of the offspring because none of the authors except Hack discussed the sex ratios.

Results

The table shows the data yielded by the search. Data were omitted which dealt with cases of artificial insemination by donor and with cases in which simultaneous extrauterine pregnancies occurred. In all three categories of data (for ovulation induced by clomiphene, gonadotrophin, and both) there was an excess of girls. Multiple births after induction of ovulation were almost all multizygotic (rather than monozygotic), so the sexes of the infants in such multiple pregnancies may be assumed to have been roughly independent. Hence the data

The sexes of infants born after induction of ovulation with clomiphene or gonadotrophin, or both

Source	Singletons		Twins		Other		All		Total	
	M	F	M	F	M	F	M	F	M	F
Clomiphene										
Adashi <i>et al</i> ⁶					2	5	36	50		
Healey and Burger ⁷							2	5		
Karow and Payne ⁸							56	68		
Total					2	5	94	123	94	123
Gonadotrophin										
Caspi <i>et al</i> ⁹	32	50	18	23	19	10	69	83		
Hack <i>et al</i> ⁵	22	25	14	32	11	11	47	68		
Lachelin <i>et al</i> ¹⁰					1	5	1	5		
Lauersen <i>et al</i> ¹¹					1	3	1	3		
Ansbacher ¹²	3	1					3	1		
Monnier <i>et al</i> ¹³					1	4	1	4		
Schenker <i>et al</i> ¹⁴					12	13	12	13		
Total	57	76	32	55	45	46	134	177	134	177
Gonadotrophin and clomiphene										
Schenker and Simha ¹⁵					2	3	2	3		
Senez and Gillet ¹⁶							27	30		
Total					2	3	29	33	29	33
Grand total									257	333

while those conceived in the middle of the fertile period are predominantly female.^{2 3} These data would be explained if maternal gonadotrophin concentrations at the time of conception partially controlled the sex of the zygote, high concentrations being associated with female conceptions.¹ If this were true then conceptions occurring after the induction of ovulation should be predominantly female. I reviewed the published reports to see whether this was so.

Methods

In reviewing the incidence of multiple births among pregnancies after induction of ovulation Wyshak compiled a large list of references,⁴ and I found further papers by (a) consulting all the issues of

may be tested by the χ^2 test. Taken separately the clomiphene group and the gonadotrophin group each showed a significant excess of female births when tested against an expected sex ratio of 0.514 (the p values being, respectively, 0.017 and 0.003). When the data were pooled the significance level was overwhelming (p=0.0002). Thus the sex ratio of infants born after induced ovulation is almost certainly low.

Discussion

The published data are consistent with the suggestion that maternal gonadotrophin concentrations at the time of conception partially control the sex of the zygote. If this were true it would explain a considerable amount of direct and indirect data previously reviewed.¹ It is not clear how gonadotrophin might affect the sex of the fetus, but it does not seem to be through sex-selective spontaneous abortion. If gonadotrophin had a deleterious effect on male zygotes then women with high gonadotrophin concentrations might be expected to have early unrecognised spontaneous

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abortions. And if this were true then women with high hormone concentrations would have a lower fecundity than other women (taking more time to become recognisably pregnant because of unrecognised spontaneous abortions). This thesis seems to be false, however, because DZ twins (who themselves tend to be conceived when gonadotrophin concentrations are high) take less, not more, time to conceive than singletons.^{17 18}

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SHORT REPORTS

Serum concentrations of 24,25-dihydroxy vitamin D in different degrees of chronic renal failure

Decreased production of 1,25-dihydroxy vitamin D in advanced renal failure may be a major factor in the pathogenesis of renal osteodystrophy.¹ Recent studies have shown that another renal metabolite, 24,25-dihydroxy vitamin D, is important in normal bone formation.² We have measured the serum concentrations of 25-hydroxy and 24,25-dihydroxy vitamin D in patients with different degrees of renal failure to provide further data concerning vitamin D metabolism in chronic renal failure.

Patients, methods, and results

Serum concentrations of 25-hydroxy and 24,25-dihydroxy vitamin D were measured in 76 patients with chronic renal failure and 30 controls. The patients comprised 26 undergoing chronic haemodialysis three times a week (including eight anephric patients), 20 with advanced renal failure not requiring haemodialysis (creatinine clearances 10-35 ml/min/1.73 m²), and 30 with early to moderate renal failure (creatinine clearances 40-80 ml/min/1.73 m²). Serum samples from the patients receiving haemodialysis were obtained immediately before dialysis. The patients had not received transfusions within six weeks before the specimens were collected. No patient was receiving vitamin D supplements or drugs known to alter vitamin D metabolism. Concentrations of 25-hydroxy and 24,25-dihydroxy vitamin D were measured by competitive protein-binding radioassays³ after preparative Sephadex LH-20 column and high-pressure liquid chromatography.

The mean ($\pm$ SEM) serum concentration of 25-hydroxy vitamin D was significantly ($p < 0.01$) lower in patients receiving haemodialysis (36.0 ± 3.8 nmol/l (14.4 ± 1.5 ng/ml)) than controls (53.8 ± 3.6 nmol/l (21.5 ± 1.4 ng/ml)). The mean concentrations in patients with advanced renal failure not requiring haemodialysis (43.5 ± 5.3 nmol/l (17.4 ± 2.1 ng/ml)) and in patients with mild to moderate renal failure (47.6 ± 3.6 nmol/l (19.0 ± 1.4 ng/ml)) did not differ from that in controls. The mean serum concentration of 24,25-dihydroxy vitamin D (figure) and the mean ratio of serum concentrations of 24,25-dihydroxy vitamin D to those of 25-hydroxy vitamin D were significantly lower ($p < 0.01$) in the patients receiving haemodialysis (1.18 ± 0.40 nmol/l (0.5 ± 0.16 ng/ml) and 0.030 ± 0.003 respectively), the patients with advanced renal failure not requiring haemodialysis (1.88 ± 0.25 nmol/l (0.75 ± 0.1 ng/ml) and 0.042 ± 0.004 respectively), and the

patients with mild to moderate renal failure (2.70 ± 0.22 nmol/l (1.1 ± 0.09 ng/ml) and 0.058 ± 0.003) compared with the controls (4.78 ± 0.30 nmol/l (1.9 ± 0.12 ng/ml) and 0.092 ± 0.004). The ratios of the two metabolites were directly correlated ($r = 0.72$, $p < 0.05$) with the creatinine clearances when data from all patients were analysed.

Mean $\pm$ SEM serum concentrations of 24,25-dihydroxy vitamin D in patients with different degrees of chronic renal failure and controls. $\circ$ = Anephric patients. Conversion: SI to traditional units—24,25-Dihydroxy vitamin D: 1 nmol/l $\approx$ 0.4 ng/ml.

Comment

Our results show that serum concentrations of 24,25-dihydroxy vitamin D are depressed in mild to moderate chronic renal failure and are low or undetectable in patients receiving dialysis. Reduced production of 1 α , 25-dihydroxy vitamin D by the diseased kidney is generally believed to be important in the pathogenesis of renal osteodystrophy, and the serum concentration of this metabolite is