Goldenhar syndrome and overlapping dysplasias, in vitro fertilisation and ovopathy

SUMMARY In contrast to the opinion of Yovich *et al.*,¹ who documented Goldenhar syndrome in one of possibly monozygous twin brothers conceived by in vitro fertilisation and embryo transfer, I suggest that ovopathy is the cause of this anomaly. The eight criteria which have to be met before a condition can be said to be caused by overripeness ovopathy are shown to be satisfied. My conclusion remains that, in general, sporadically occurring Goldenhar variants, as distinct from familial cases, should be considered to be just casualties in the broad 'continuum of reproductive wastage' seen in high risk conceptions, one of which is IVF. This concept increases our understanding of human variation not satisfactorily explained by Mendelian inheritance.

The Goldenhar syndrome² (GS) and its variants, also referred to as the Goldenhar anomalad or the oculoauriculovertebral (OAV) dysplasias, occupy a central position in the broad spectrum of overlapping anomalies related to the eyes, ears, face, and vertebral column. GS was the first congenital anomaly presumed to be caused by overripeness ovopathy in humans.^{3,4} This hypothesis, proposed in 1968, was built up on the following.

- (1) Case studies, including the documented history of a proband, a sixth child, conceived despite the use of the rhythm method of contraception on the 30th day of a prolonged menstrual cycle during the post-partum restoration of the ovulatory pattern.
- (2) The clear parallels with the deficiencies in tissue differentiation and organogenesis found in animals after preovulatory⁵ and postovulatory⁶ ageing of the egg, often leading to concordant and more specifically to discordant monozygous (MZ) twins.
- (3) The numerous and fluent transitions to other syndromes and congenital dysplasias, such as hemifacial microsomia, asymmetrical crying face with congenital eye defects, Duane retraction syndrome, Wildervanck syndrome, Klippel-Feil anomaly, and many others, that often can not be distinguished diagnostically.

- (4) The mainly sporadic occurrence which is difficult to reconcile with Mendelian inheritance.
- (5) The wide variation of associated anomalies.

This line of thought has been substantiated by both a retrospective and a prospective study showing that the (preovulatory) hypothermic phase of the conceptional cycle is longer and that the temperature rise is slower in mothers of infants with congenital dysplasias (for example, of the face) than in those of normal term infants.^{7,8} In fact, cases of OAV dysplasias have been reported in singletons as well as in concordant or discordant MZ twins, in which gametopathy has been, or should be, considered as the presumed cause due to a non-optimum conception, as will be seen later.

Therefore, it is not just a strange coincidence that GS is also the first congenital anomaly reported following in vitro fertilisation (IVF) and embryo transfer (ET), even though any causal relationship was denied either with the method of conception or with possible MZ twinning.¹ This treatment was carried out because of infertility due to polycystic ovary disease, and it resulted in male triplets. One of these was affected by GS but a possibly MZ twin brother was not ($p < 0.001$ for dizygosity, except for the Fy(a) antigen).

In the present paper I contest the statements of Yovich *et al.*¹ that this anomaly is not causally related either to (possibly) MZ twinning or to the techniques applied (IVF and ET). After all, many MZ twins have been reported after IVF⁹ and discordant

ance is a striking phenomenon in GS.¹⁰⁻¹² In addition, increased fetal loss, abnormal embryonic development, and some degree of microphthalmia have been reported in nearly half of the offspring after IVF in rats¹³; there is also a 90% failure rate of implantation of human IVF embryos, a 30% abortion rate, and a high rate of chromosomal abnormalities in preimplantation embryos.^{14 15} In fact, the follicular fluid of endocrinologically normal women has been shown to contain more inhibin activity and lower oestrogen and progesterone levels when stimulated than when not.¹⁶ Superovulation therapy, of course, 'forces' the development of a spectrum of preovulatory oocytes which are in different phases of maturation at the moment that the human chorionic gonadotrophin (HCG) dose is given; if the timing is optimal for some, it will be too late or too early for others and so eggs less likely to undergo further normal development will be produced.¹⁷ It is true that no increase in congenital anomalies and chromosomal aberrations above that found after conceptions *in vivo* has been observed, and no constant pattern of anomalies has emerged suggesting a specific underlying defect in the treatment,⁹ but comparison of the outcome of pregnancy after IVF with the outcome after *in vivo* conceptions at high risk¹⁸ may be informative about fundamental aspects of developmental processes and tissue disruption.

Although the necessary epidemiological data on OAV dysplasias and Goldenhar variants are not always available, additional support for overripeness ovopathy being the cause has been found in more recent published reports.¹⁹ I will show this by means of the eight criteria that have been deduced from animal ageing egg research which have to be satisfied to substantiate this aetiology.

The overripeness ovopathy theory

In both animals and humans, delay of either ovulation or fertilisation leads to meiotic (and mitotic) non-disjunction and also to failed cell interaction, impeded morphogenetic movements, tissue disruption, and altered differentiation schedules. This results in embryonic or fetal death, growth retardation, differential growth, changes in the respective positions of cells shaping the organs and the body, that is, dysplasias of one or more developmental fields (polymorphic syndromes), or functional deficits in the neonate, infant, or even adult. This constitutes a clear and recognised 'continuum of reproductive casualties'.^{7 8 20 21} This disturbance starts from the ovum and induces a slow down of the rapid, sequential, and considerable

growth in one or more developmental fields instead of at one or another critical stage of embryonic or fetal development, as is generally believed in the case of developmental anomalies. Either ovulation may be delayed during the transitional stages of reproductive life (adolescence, premenopause, postpartum, weaning, 'ovulatory' and 'anovulatory' seasons), or fertilisation may occur in the case of inconsistent and ineffective contraception.^{18 22}

The overripeness ovopathy criteria

(1) SPORADIC OCCURRENCE

That occurrence of OAV dysplasias or the Goldenhar variants is mainly sporadic is generally agreed.²³ It is true that in some instances of limbal dermoids and of first and second branchial arch syndromes meticulous family studies have disclosed signs in relatives, pointing to recessive and dominant genetic factors.²⁴⁻²⁷ It should be pointed out that a maternal constitution may predispose to recurrent ovopathy and to mimicry of Mendelian inheritance,¹⁸ but familial cases often look like 'pseudo-OAV', dysplasias caused by mutant alleles (genocopies), which are difficult to distinguish, particularly when the clinical signs are less marked and less typical.²⁸ In every case, two clearly autosomal dominant disorders emerge from the 'hereditary ear adysplasia-renal dysplasia syndrome', namely branchio-oto-renal (BOR) dysplasia and branchio-oto (BO) dysplasia.²⁴⁻²⁷ These genocopies, of course, should be separated from the Goldenhar dysplasias caused by overripeness ovopathy.

(2) CONCORDANT AND DISCORDANT OCCURRENCE IN MZ TWINS

As in the animal experiments on delayed ovulation (preovulatory overripeness ovopathy⁵) and delayed fertilisation (postovulatory overripeness ovopathy⁶), OAV dysplasias have been noticed frequently in both concordant and discordant MZ twins.^{4 10-12} Therefore, the denial of Yovich *et al*¹ of a causal relationship between MZ twinning and OAV dysplasia, albeit an indirect one, is hard to substantiate. In fact, an increased incidence of identical twins has been presumed after IVF⁹ and the increase of early embryonic malformations and developmental field complexes such as GS in one or both MZ twins has been the stimulus for considering a common aetiology for both MZ twinning and the early malformation problem.¹¹ Overripeness ovopathy could lead to one or the other^{4 19} and therefore GS after IVF¹ may be considered as just a casualty in the broad 'continuum of reproductive wastage' also seen in other high risk conceptions.¹⁸

(3) ACCOMPANIMENT OF MULTIPLE CONGENITAL ANOMALIES

As in the animal experiments on ageing of the egg, a wide spectrum of associated anomalies, not restricted to the derivatives of the primordia for the eyes, first and second branchial arch structures, or notochord, have been reported in OAV dysplasias.²³ Central nervous system anomalies in all their varieties often accompany the OAV dysplasias or the so-called maxillomandibular neuro-cristopathies,²⁸ for example, hypoplasia or aplasia of one or more nuclei in the brain stem and their corresponding cranial nerves with sensory, sensorineural, and motor deficiencies.²⁹ The same is true for cardiovascular, pulmonary, renal, visceral, and skeletal dysplasias (oral clefts, polydactyly), etc.^{23 29 31} These associated anomalies and their severity do not appear to follow a specific distribution, as would be expected if genetically determined, but rather the casual distribution in the general population.³² The unwieldy nature of these malformations appears to be dependent on the disruption in one or more developmental fields and also explains the overlap with the CHARGE association,³³ the MURCS association,³⁴ the immunodeficiencies,³⁵ idiopathic hypoparathyroidism and thymic dysplasia (DiGeorge syndrome³⁶ or branchial dysembryogenesis³⁷), and many other defects. Therefore, each one of the infinite number of possible variations either assumes an eponym or is classified with the first and second branchial arch malformations, a spectrum of dysplasias in which anomalies of the eyes, ears, face, and vertebral column appear to be markers rather than obligatory parts of them.^{38 39} This complex group of patients of course "do not necessarily represent formal genesis syndromes or nosologic entities different from the other types"^{31 36} and introduction of the over-ripeness ovopathy theory here supports the 'lumping' rather than the 'splitting' attitude.

(4) ACCOMPANIMENT OF NON-SPECIFIC CHROMOSOMAL ABERRATIONS

As in dysplastic fetuses resulting from experimental ageing of the egg in animals,²¹ subjects affected by OAV dysplasias are sometimes found to have non-specific chromosomal aberrations, for example, 47,XXX,⁴⁰ 49,XXXXX,⁴¹ 46,XX/47,XX,+7 mosaicism,⁴² 47,XXY, 49,XXXXY, 46,Bp- (twice), 46,18q-, and other structural defects.²⁷

(5) ACCOMPANIMENT OF GONADAL DYSGENESIS

In animal ovopathy experiments,⁶ the primordial germ cells exhibit degenerative features even when only slightly affected by the ageing process. They

multiply slowly and enter the gonadal folds only in small numbers or not at all and this results in dysgenesis of the gonads. Although few researchers have paid attention to this area, cryptorchidism, ovarian anomalies, and other genital malformations have occasionally been mentioned in this complex group of Goldenhar variants.^{33 34 43 44} Unimpaired fertility has been claimed for GS in a 'natural history' of the disorder,⁴⁵ but this conclusion is questionable as it was based on 24 patients of whom only two were adults, a female of 37 and a male of 58 years without any data concerning their reproductive performance.

(6) ASSOCIATION OF SUBOPTIMAL REPRODUCTIVE STATE OF THE PROBAND'S MOTHER

Subjects with OAV dysplasias born to mothers with casual or constitutional impairment of the ovulatory pattern or difficulty in conceiving have been reported.^{1 46} In spina bifida cystica and occulta, nearly half of the mothers appear to have been reported to have had a history of irregular cycles, long periods of infertility, menorrhagia, and severe dysmenorrhoea, and some showed an increased rate of abortion, stillbirths, and even recurrent neural tube defects.⁴⁷ The same suboptimal reproductive state has been established in mothers of oral cleft children.⁴⁸

(7) ASSOCIATION WITH HIGH RISK CONCEPTIONS

There are case reports of OAV dysplasias in which other non-optimum conceptions are presumed, for example, where an insulin dependent diabetic mother is concerned,^{49 50} when conception has taken place during use or immediately after stopping the contraceptive pill,^{36 42 51 52} or otherwise unplanned pregnancies.^{3 51} This is in line with the over-ripeness ovopathy predictions, as are also the prolonged preovulatory phase and the slower temperature rise in the conceptional cycle of mothers of infants with congenital dysplasias (particularly of the face) compared with those of normal term infants.^{7 8}

(8) ASSOCIATION WITH VARIOUS COMPLICATIONS OF PREGNANCY, PARTURITION AND NEONATAL LIFE

Among the complications commonly reported in OAV dysplasias, evidently the very early ones, such as ectopic pregnancies (tubal pregnancies and placenta praevia), MZ twinning, and vaginal bleeding in very early pregnancy, are narrowly related to the early condition of the fertilised egg and predate the formation of the relevant facial and vertebral structures in a three to five week embryo. Therefore, a reconstruction of the cause and effect may

show ovopathy to be the primordial insult and the common cause of both dysmorphogenesis and complications in early as well as late pregnancy and the neonatal period.

Conclusions

The arguments of Yovich *et al*¹ that the condition in their proband with GS is not causally related either to (possibly) MZ twinning or to IVF remain speculative. MZ twinning has been reported frequently after IVF and in connection with Goldenhar dysplasia. In addition, GS also shows the same tendency to discordant MZ twinning and to disruption in the developmental fields of the primordial eyes, branchial arch structures, and notochord, as shown by experimental animal research on ageing ova. GS also satisfies the eight criteria which have to be met before a condition can be said to be caused by overripeness ovopathy. The casual association with non-specific chromosomal aberrations and with (discordant) MZ twinning explicitly dates the timing and type of insult, assigning it to the meiotic and first mitotic divisions instead of to the third to fifth week of pregnancy as is usually thought. Therefore, I maintain that the (mainly) sporadic OAV dysplasias, as distinct from the (mainly) familial cases which are genetically determined, should be considered as casualties in the broad 'continuum of reproductive wastage' seen after high risk conceptions, one of which is IVF.

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This paper was shown to Dr Yovich and colleagues who reply on page 644.