

Clefts in Quintuplets—A Case Report

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A report of *clefting* in three *siblings* of *quintuplets*, following treatment with *Pergonal*, is presented. It is suggested that the varying degrees of the abnormality may be related to cramped intra-uterine conditions or differing pressures at a critical developmental stage. To our knowledge, no previous reports of congenital abnormalities associated with Pergonal therapy exist, and we feel that the causal relationship should be explored using a suitable animal model.

Introduction

Clefts of the lip (with or without palatal clefting) are developmentally different from isolated median cleft palates (Fraser, 1970, and Spriestersbach et al., 1973). In most cases, clefts of the lip have a multifactorial etiology and are said to date from an earlier developmental stage than median palatal clefts (Lis et al., 1956). The degree of severity of clefts may vary from one child to another even within identical twin sibships (Pruzansky et al., 1970 and Ross and Coupe, 1965). Several explanations have been suggested for this variance, including the duration or potency of teratogenic stimuli, intrauterine posture, or local differences in first branchial arch vascular supply (Poswillo, 1975) or placentation (Kraus et al., 1959). We wish to present a case of Pergonal-induced quintuplets, three of whom had facial clefting of varying degrees of severity.

Case report

The fertilization occurred during the 4th cycle of a course of Pergonal and mid-cycle human chorionic gonadotrophin (Thompson and Hansen, 1970). At the time of conception, the mother, a healthy thirty-two-year-old

woman with a history of primary amenorrhea and sterility, was receiving 90 ampules of Pergonal per month (each ampule contained 75 I.U. of human chorionic gonadotrophin). The parents were unrelated, and there was no history of facial clefts. A previous Pergonal-induced pregnancy had resulted in the birth of a healthy, full-term male infant in 1972, and there had been a spontaneous abortion in 1976, also after induction of ovulation with Pergonal. There had been no maternal illness during the pregnancy. A multiple birth was suspected at the beginning of the second trimester, and the presence of at least four fetuses was confirmed radiologically. A fifth was suspected. Spontaneous onset of labour occurred at 34 weeks.

Five infants (three boys and two girls), each with his own healthy placenta and chorion-amniotic sac, were delivered by lower-segment caesarian section under general anaesthesia. There was no birth asphyxia. Two boys, A weighing 1670 g. and B weighing 1580 g., were normal. The third boy C, weighing 2020 g., and both girls, D weighing 1850 g. and E weighing 1820 g., had clefts of varying degrees of severity.

Girl E had a left-sided cleft of the lip and alveolar process, with an intact palate (Figures 1 A and B). Girl D had a bilateral cleft of the lip and alveolar ridge with an intact palate (Figures 2 A and B). Boy C had a bilateral cleft lip, alveolus, and palate (Figures 3 A-C). All the infants were tube-fed initially. Neither of the girls with clefts had sucking or swallowing difficulties. The worst-

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FIGURE 1A. Face of girl E with unilateral cleft lip and alveolar process.



FIGURE 2A. Face of girl D with bilateral cleft of lip and alveolar process. Note the intact palate and the protrusion of premaxilla.

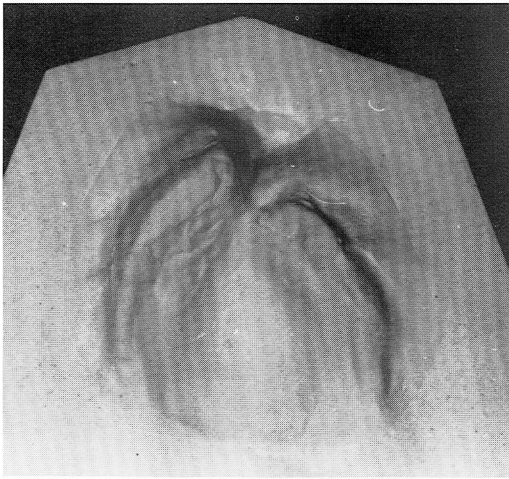


FIGURE 1B. Cast of her upper jaw.

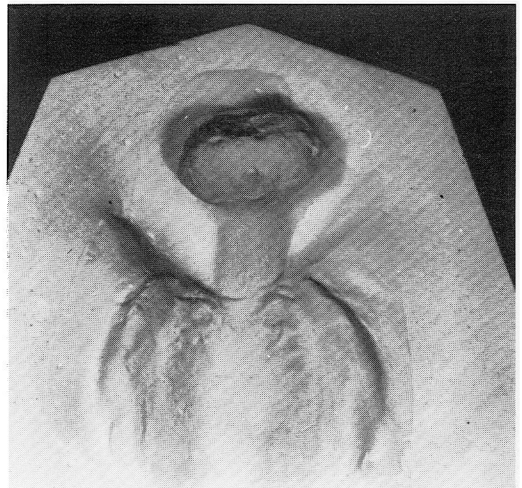


FIGURE 2B. Cast of her upper jaw.

affected boy was fitted with a palatal obturator to enable him to suck satisfactorily. There were no other neonatal problems and, at the time of discharge, all five infants showed appropriate weight gain and were developing normally.

Discussion

These quintuplets demonstrate varying degrees of clefting, an observation which concurs with that of Pruzansky et al. (1970) with

regard to twin pregnancies. It is tempting to suggest that the varying expression of clefting is related to differing degrees of contact between the developing face and thoracic viscera between the 4th and 8th weeks (Poswillo, 1975), but it would not account for the consistently higher male incidence of clefts.

Meskin et al. (1968) mentioned that, within the three types of clefts, there are quantitative degrees. They proposed a hypothetical model of differential palatal development between



FIGURE 3A. Face and profile of boy C with complete bilateral cleft lip and palate.



FIGURE 3B. Note the maxillary protrusion and the ulceration of the nasal mucosa prior to insertion of an obturator.

the sexes to explain this gradation. According to their hypothesis, primary and secondary palatal formation is more advanced in males than in females. This was confirmed by Burdi and Silvey (1969) in their studies on human embryos, where they found that females lag behind males in palatal closure. At the time of teratogenic action, females are at an earlier stage of development of the primary and sec-

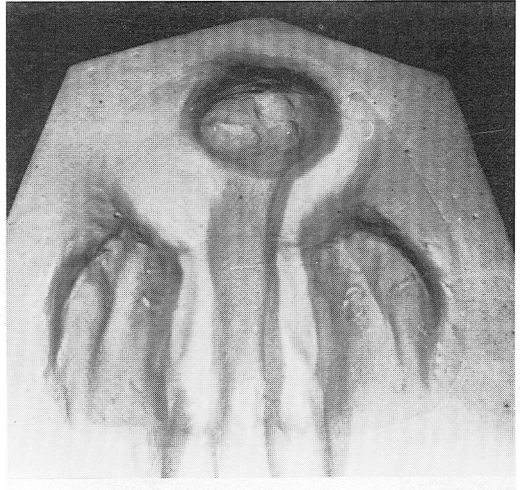


FIGURE 3C. Cast of his upper jaw.

ondary palate than are males. Therefore, females would predominate in both extent and numbers of clefts (Meskin et al., 1968). This hypothesis explains the 2:1 ratio that we found between the girls and the boy, but it conflicts with the severity of the cleft in the boy as compared to his two sisters.

The risk of clefting may be increased in a multiple pregnancy because of intra-uterine cramping or because of the underlying infertility, as has been suggested by Dyson and Kohler (1973) and by James (1973). Ornoy (1979), in addition, has suggested that the pressures on the amniotic fluid encompassing each fetus may increase as the fetal position lowers in the uterus. It has been repeatedly shown that experimental reduction of amniotic fluid volume in rats causes cleft palate, as well as other congenital defects (Demyer and Baird, 1969).

No reports of congenital abnormality attributable to Pergonal have come to hand, confirming Foster's (1978) assertion, that there were not "any congenital oral defects following the use of fertility drugs in Birmingham". However, in the light of this presentation, it is our view that the question as to whether Pergonal itself contributes directly or indirectly to clefting requires re-examination using an appropriate animal model.

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