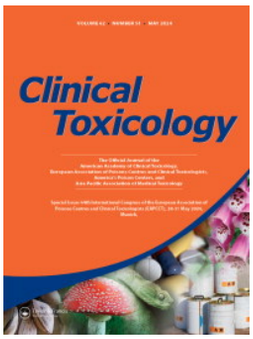

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EDITORIAL

PURSUING TERATOGENIC CAUSES OF MULTIPLE CONGENITAL CONTRACTURES

Editorial

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One of the major issues surrounding any new drug is its teratogenic potential. Ideally, teratogenicity should be identified before marketing, especially if women of reproductive age are potential users of the drug. An obvious avenue to try and establish the teratogenic potential of a new product is the use of animal studies. The failure to detect the thalidomide embryopathy has led to a nihilistic attitude of the medical community to animal studies. However, in retrospect all known human teratogens (with the exception of coumadins) have been shown to be teratogenic in animals. In at least one case (retinoic acid) observations in animals probably prevented a disaster similar in magnitude to that of thalidomide. Aside from the predictive value of animal studies, animal models can provide valuable information on the mechanism of teratogenic agents and the pathogenesis of some malformations. Multiple congenital contractures (arthrogryposis multiplex congenital MCC) is a case in point. Much of what is known about the pathogenesis of MCC is based on observations of naturally occurring MCC in domestic animals and on animal models (1).

MCC was first described in 1841 by Adolph Otto (2). Since then, it has been reported numerous times, under a variety of names and as a part of many syndromes. The term "arthrogryposis" was first coined in 1923 by Stern and has gained widespread acceptance (1). As with many terms rooted in tradition, the term arthropgryposis has led to confusion surrounding the etiology and the definition of the clinical entity. More than a dozen terms have been applied to conditions in which MCC is the primary defect. Though a variety of definitions exist, it is best described as congenital fixation of one or more joints, in either extension or flexion, with associated skeletal abnormalities. What this definition points out is that arthrogryposis is not a single disease, but is the final clinical condition for a whole array of pathological changes that occur in utero. It is for this reason that the term "multiple congenital contractures" has been proposed as preferred terminology for the malformation (3) Arthrogryposis or MCC is not a diagnosis but a clinical description (4).

In animals, the causes of MCC include genetic defects, viruses affecting the CNS (e.g. Akabane virus), mechanical fixation of joints, toxins, and a variety of

plant alkaloids (5). A similar list exists for the human condition. Due to the variability of the syndrome, which may occur alone or with other major birth defects, the actual cause is often difficult to elucidate. However, it is important to make as accurate a diagnosis as possible so that appropriate management can be initiated (6) and, in cases which may have a genetic basis, appropriate counselling for future pregnancies can be made (4). The issue of teratogenic insults resulting in MCC has yet to be resolved or explored in depth. In a series of more than 350 patients, only 15 had any association, however tenuous, with a teratogenic insult (7). Of these, only two were associated with the ingestion of a drug or toxin (methocarbamol; alcohol). Two other case reports have been published; one suggesting an association between curare administration in a pregnant woman with tetanus (8) and the other in association with chronic malathion exposure during pregnancy (9).

It is generally believed that the multiple etiologic factors leading to MCC result in loss of fetal movement with subsequent abnormal joint development (1, 4, 10, 11). The theoretical basis of the pathogenesis of MCC is based largely on animal models and subsequent clinical observations in humans. The first experimental model of arthrogryposis was described in 1962 with the injection of *d*-tubocurarine into chick embryos (12) . This consistently resulted in ankylosis of skeletal joints, presumably the result of the paralysis. Similar studies were subsequently performed in rats with the same results (13). Amniocentesis in rats also produced cleft palate and limb contractures (14). These and other studies have provided support for the hypothesis that MCC is caused by the loss of fetal movement which may accompany neurological or muscular disease or mechanical restriction of the fetus (e.g. oligohydramnios). Clinical findings in man have correlated well with these findings (1, 3, 10). In many conditions where one would expect loss of fetal movement, MCC is known to occur more often than in the general population: congenital muscular dystrophy, myasthenia gravis, spina bifida, abnormalities of amniotic fluid production (e.g. Potter's syndrome), amyoplasia, etc. (1, 6, 10, 11, 15). However, in naturally occurring cases of

MCC, neuropathic, neuromuscular, or myopathic disorders are commonly identified (1, 3, 4, 10, 11) and are presumed to lead to loss of fetal movement. The contribution of the primary pathologic condition to the expression of MCC versus the contribution of loss of movement is not clear. Thus, the potential teratogenic role of agents which could affect fetal movement at a critical stage without causing primary pathologic changes is unclear.

In this issue of Clinical Toxicology, Panter et al. describe the use of real-time ultrasound to observe fetal movement after ingestion of poison-hemlock in sheep. The same group has shown previously that Conium maculatum is capable of causing athrogryposis in cattle and pigs (16, 17). In conjunction with the present study, they demonstrated that poison-hemlock given to pregnant ewes during gestation days 30-60 (approximate equivalent to the end of first trimester and beginning of second in humans) produced mild limb deformities (18). What is exciting in this work the possibility of an animal model of monitoring fetal movement with ultrasound. The possibility of using real-time ultrasound as a research tool and perhaps as a way of predicting the presence or increased likelihood of arthrogrypotic deformities in humans is tantalizing. Before this can be realized, however, the association between loss of fetal movement and the occurrence of the birth defect must be expanded to a cause-effect relationship. As the authors point out, more work is needed to delineate the relations between the time and extent of loss of fetal movement and teratogenic effects. Unfortunately, in the present animal model, the malformations are mild and resolved spontaneously. It is difficult to classify the lesions as "arthrogrypotic" with confidence. It needs to be demonstrated that the loss of movement does not occur independently of the occurrence of malformations and that similar malformations do not occur when fetal movement is normal. As a further control, another xenobiotic which causes similar maternal illness and distress but does not cause malformations must be shown to have no effect on fetal movement.

Normal fetal movement patterns throughout gestation have been delineated (19) and the use of ultrasound to prenatally diagnose a lethal syndrome of

MCC(20) has been reported. Ultrasonic findings included subcutaneous edema and decreased limb movements. However the authors state that the ultrasonic signs are not pathognomonic and a definitive diagnosis is not possible without previous affected fetuses in the family. It has been suggested that looking for decreased fetal activity and little change in position between 19 and 24 weeks of gestation using real-time ultrasound may be useful in cases where there is a familial history of MCC (4, 21). Clearly the loss of fetal movement needs to be temporally associated with joint and muscular development to produce contractures (1).

There are many questions remaining to be answered concerning the degree and length of time of loss of fetal movement in causing MCC before the full role of teratogens in this syndrome can be understood. Recent technological developments in ultrasound will certainly increase our ability to employ this technique for exploring mechanisms of reproductive toxicology.

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