

Higher BP, Fasting Glucose Found in IVF Children

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Children born as a result of in vitro fertilization have significantly higher blood pressure and fasting glucose levels than do those conceived naturally—a finding suggestive of fetal programming during an early developmental window, Dr. Manon Ceelen and colleagues reported.

Although the possible mechanism be-

hind this finding remains unknown, the study “underscores the importance of the continuing worldwide monitoring of post-natal development of IVF children,” Dr. Ceelen and her coauthors wrote in the *Journal of Clinical Endocrinology and Metabolism* (2008 Feb. 19 [doi:10.1210/jc.2007-2432]).

Dr. Ceelen and her coauthors of the Free University Medical Center, Amsterdam, compared the cardiometabolic measurements of 225 IVF and 225 naturally

conceived children (average age, 12 years).

The parents of all the children had been part of a Dutch study on the long-term health effects of hormone stimulation in 26,400 subfertile women. Of this group, 20,000 women received IVF treatment.

Compared with naturally conceived children, those conceived through IVF weighed significantly less on average at birth (3.2 vs. 3.4 kg).

In addition, there were significantly

more preterm infants among the IVF group (29 vs. 6).

Average systolic blood pressure was significantly higher in IVF children than in the control group (109 mm Hg vs. 105 mm Hg); mean diastolic blood pressure was also significantly higher in the IVF group (61 mm Hg vs. 59 mm Hg).

Children born via IVF were twice as likely as those naturally conceived were to have a systolic blood pressure of at least 114 mm Hg and to have a diastolic blood pressure of at least 65 mm Hg.

Those in the IVF group had significantly greater average sum of skinfolds measurement (40 mm vs. 37 mm), although there were no significant differences in weight or body mass index between the groups.

Significantly higher mean fasting glucose measurements were seen in the IVF group (5 mmol/L vs. 4.8 mmol/L).

IVF children were 2.5 times more likely to have a fasting glucose level of at least 5.2 mmol/L.

‘It cannot be excluded that raised blood pressure after IVF may be amplified throughout life, as blood pressure is known to track from childhood into adult life.’

These relationships remained significant even after the investigators adjusted for confounders (birth weight, gestational age, sum of skinfolds measurement, parity, and the cause of the mother’s subfertility).

Although the differences in blood pressure appear small on an individual level, they could have significant health implications on a population level, the investigators wrote.

“A slight increase in blood pressure is associated with a remarkably increased risk of developing cardiovascular disease. ... Furthermore, it cannot be excluded that raised blood pressure after IVF may be amplified throughout life, as blood pressure is known to track from childhood into adult life,” they noted.

The authors could not explain the observed relationships between IVF and cardiometabolic status. Both population and animal studies show a link between prenatal environment and early gestational development.

For instance, maternal malnutrition in early pregnancy has been linked to later cardiovascular disease in the offspring. “Preconceptional undernutrition has been associated with the precocious activation of the hypothalamo-pituitary-adrenal axis,” the authors wrote.

They said this premature activation might be associated with fetal programming effects.

However, the investigators wrote, “it remains to be elucidated whether increased blood pressure among IVF children originates from early prenatal life adaptations mediated through neuroendocrine pathways related to the HPA axis and/or through one of the unidentified mechanisms.”

The adverse reactions that most frequently resulted in clinical intervention (e.g., rest periods, withdrawal from study) were local skin and application site reactions; 10% (19/185) of subjects received rest periods. The average number of doses not received per subject due to rest periods was 7 doses with a range of 2 to 22 doses; 79% of subjects (15/19) resumed therapy after a rest period. Overall, in the clinical studies, 2% (4/185) of subjects discontinued for local skin/application site reactions. In the sBCC studies, 17 of 1266 (1.3%) Aldara-treated subjects developed treatment site infections that required a rest period and treatment with antibiotics. **6.3 Clinical Trials Experience: External Genital Warts** In controlled clinical trials for genital warts, the most frequently reported adverse reactions were local skin and application site reactions. Some subjects also reported systemic reactions. Overall, 1.2% (4/327) of the subjects discontinued due to local skin/application site reactions. The incidence and severity of local skin reactions during controlled clinical trials are shown in the following table.

Table 8: Local Skin Reactions in the Treatment Area as Assessed by the Investigator (External Genital Warts)

	Aldara Cream				Vehicle			
	Females n=114		Males n=156		Females n=99		Males n=157	
	All Grades*	Severe	All Grades*	Severe	All Grades*	Severe	All Grades*	Severe
Erythema	74 (65%)	4 (4%)	90 (58%)	6 (4%)	21 (21%)	0 (0%)	34 (22%)	0 (0%)
Erosion	35 (31%)	1 (1%)	47 (30%)	2 (1%)	8 (8%)	0 (0%)	10 (6%)	0 (0%)
Excoriation/Flaking	21 (18%)	0 (0%)	40 (26%)	1 (1%)	8 (8%)	0 (0%)	12 (8%)	0 (0%)
Edema	20 (18%)	1 (1%)	19 (12%)	0 (0%)	5 (5%)	0 (0%)	1 (1%)	0 (0%)
Scabbing	4 (4%)	0 (0%)	20 (13%)	0 (0%)	0 (0%)	0 (0%)	4 (3%)	0 (0%)
Induration	6 (5%)	0 (0%)	11 (7%)	0 (0%)	2 (2%)	0 (0%)	3 (2%)	0 (0%)
Ulceration	9 (8%)	3 (3%)	7 (4%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Vesicles	3 (3%)	0 (0%)	3 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

*Mild, Moderate, or Severe

Remote site skin reactions were also reported. The severe remote site skin reactions reported for females were erythema (3%), ulceration (2%), and edema (1%); and for males, erosion (2%), and erythema, edema, induration, and excoriation/flaking (each 1%). Selected adverse reactions judged to be probably or possibly related to Aldara Cream are listed below.

Table 9: Selected Treatment Related Reactions (External Genital Warts)

	Females		Males	
	Aldara Cream n=117	Vehicle n=103	Aldara Cream n=156	Vehicle n=158
Application Site Disorders:				
Application Site Reactions				
Wart Site:				
Itching	38 (32%)	21 (20%)	34 (22%)	16 (10%)
Burning	30 (26%)	12 (12%)	14 (9%)	8 (5%)
Pain	9 (8%)	2 (2%)	3 (2%)	1 (1%)
Soreness	3 (3%)	0 (0%)	0 (0%)	1 (1%)
Fungal Infection*	13 (11%)	3 (3%)	3 (2%)	1 (1%)
Systemic Reactions:				
Headache	5 (4%)	3 (3%)	8 (5%)	3 (2%)
Influenza-like symptoms	4 (3%)	2 (2%)	2 (1%)	0 (0%)
Myalgia	1 (1%)	0 (0%)	2 (1%)	1 (1%)

*Incidence reported without regard to causality with Aldara Cream.

Adverse reactions judged to be possibly or probably related to Aldara Cream and reported by more than 1% of subjects included: **Application Site Disorders:** burning, hypopigmentation, irritation, itching, pain, rash, sensitivity, soreness, stinging, tenderness. **Remote Site Reactions:** bleeding, burning, itching, pain, tenderness, tinea cruris. **Body as a Whole:** fatigue, fever, influenza-like symptoms. **Central and Peripheral Nervous System Disorders:** headache. **Gastro-Intestinal System Disorders:** diarrhea. **Musculo-Skeletal System Disorders:** myalgia. **6.4 Clinical Trials Experience: Dermal Safety Studies** Provocative repeat insult patch test studies involving induction and challenge phases produced no evidence that Aldara Cream causes photoallergenicity or contact sensitization in healthy skin; however, cumulative irritancy testing revealed the potential for Aldara Cream to cause irritation, and application site reactions were reported in the clinical studies [see *Adverse Reactions* (6)]. **6.5 Postmarketing Experience** The following adverse reactions have been identified during post-approval use of Aldara Cream. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. **Body as a Whole:** angioedema. **Cardiovascular:** capillary leak syndrome, cardiac failure, cardiomyopathy, pulmonary edema, arrhythmias (tachycardia, atrial fibrillation, palpitations), chest pain, ischemia, myocardial infarction, syncope. **Endocrine:** thyroiditis. **Hematological:** decreases in red cell, white cell and platelet counts (including idiopathic thrombocytopenic purpura), lymphoma. **Hepatic:** abnormal liver function. **Neuropsychiatric:** agitation, cerebrovascular accident, convulsions (including febrile convulsions), depression, insomnia, multiple sclerosis aggravation, paresis, suicide. **Respiratory:** dyspnea. **Urinary System Disorders:** proteinuria. **Skin and Appendages:** exfoliative dermatitis, erythema multiforme, hyperpigmentation. **Vascular:** Henoch-Schönlein purpura syndrome

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy Pregnancy Category C: Note: The Maximum Recommended Human Dose (MRHD) was set at 2 packets per treatment of Aldara Cream (25 mg imiquimod) for the animal multiple of human exposure ratios presented in this label. If higher doses than 2 packets of Aldara Cream are used clinically, then the animal multiple of human exposure would be reduced for that dose. A non-proportional increase in systemic exposure with increased dose of Aldara Cream was noted in the clinical pharmacokinetic study conducted in actinic keratosis subjects [see *Clinical Pharmacology* (12.3)]. The AUC after topical application of 6 packets of Aldara Cream was 8 fold greater than the AUC after topical application of 2 packets of Aldara Cream in actinic keratosis subjects. Therefore, if a dose of 6 packets per treatment of Aldara Cream was topically administered to an individual, then the animal multiple of human exposure would be either 1/3 of the value provided in the label (based on body surface area comparisons) or 1/8 of the value provided in the label (based on AUC comparisons). The animal multiples of human exposure calculations were based on weekly dose comparisons for the carcinogenicity studies described in this label. The animal multiples of human exposure calculations were based on daily dose comparisons for the reproductive toxicology studies described in this label. Systemic embryofetal development studies were conducted in rats and rabbits. Oral doses of 1, 5 and 20 mg/kg/day imiquimod were administered during the period of organogenesis (gestational days 6 – 15) to pregnant female rats. In the presence of maternal toxicity, fetal effects noted at 20 mg/kg/day (577X MRHD based on AUC comparisons) included increased resorptions, decreased fetal body weights, delays in skeletal ossification, bent limb bones, and two fetuses in one litter (2 of 1567 fetuses) demonstrated exencephaly, protruding tongues and low-set ears. No treatment related effects on embryofetal toxicity or teratogenicity were noted at 5 mg/kg/day (98X MRHD based on AUC comparisons). Intravenous doses of 0.5, 1 and 2 mg/kg/day imiquimod were administered during the period of organogenesis (gestational days 6 – 18) to pregnant female rabbits. No treatment related effects on embryofetal toxicity or teratogenicity were noted at 2 mg/kg/day (1.5X MRHD based on BSA comparisons), the highest dose evaluated in this study, or 1 mg/kg/day (407X MRHD based on AUC comparisons). A combined fertility and peri- and post-natal development study was conducted in rats. Oral doses of 1, 1.5, 3 and 6 mg/kg/day imiquimod were administered to male rats from 70 days prior to mating through the mating period and to female rats from 14 days prior to mating through parturition and lactation. No effects on growth, fertility, reproduction or post-natal development were noted at doses up to 6 mg/kg/day (87X MRHD based on AUC comparisons), the

highest dose evaluated in this study. In the absence of maternal toxicity, bent limb bones were noted in the F1 fetuses at a dose of 6 mg/kg/day (87X MRHD based on AUC comparisons). This fetal effect was also noted in the oral rat embryofetal development study conducted with imiquimod. No treatment related effects on teratogenicity were noted at 3 mg/kg/day (41X MRHD based on AUC comparisons). There are no adequate and well-controlled studies in pregnant women. Aldara Cream should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **8.3 Nursing Mothers** It is not known whether imiquimod is excreted in human milk following use of Aldara Cream. Because many drugs are excreted in human milk, caution should be exercised when Aldara Cream is administered to nursing women. **8.4 Pediatric Use** AK and sBCC are not conditions generally seen within the pediatric population. The safety and efficacy of Aldara Cream for AK or sBCC in patients less than 18 years of age have not been established. Safety and efficacy in patients with external genital/perianal warts below the age of 12 years have not been established. Aldara Cream was evaluated in two randomized, vehicle-controlled, double-blind trials involving 702 pediatric subjects with molluscum contagiosum (MC) (470 exposed to Aldara; median age 5 years, range 2-12 years). Subjects applied Aldara Cream or vehicle 3 times weekly for up to 16 weeks. Complete clearance (no MC lesions) was assessed at Week 18. In Study 1, the complete clearance rate was 24% (52/217) in the Aldara Cream group compared with 26% (28/106) in the vehicle group. In Study 2, the clearance rates were 24% (60/253) in the Aldara Cream group compared with 28% (35/126) in the vehicle group. These studies failed to demonstrate efficacy. Similar to the studies conducted in adults, the most frequently reported adverse reaction from 2 studies in children with molluscum contagiosum was application site reaction. Adverse events which occurred more frequently in Aldara-treated subjects compared with vehicle-treated subjects generally resembled those seen in studies in indications approved for adults and also included otitis media (5% Aldara vs. 3% vehicle) and conjunctivitis (3% Aldara vs. 2% vehicle). Erythema was the most frequently reported local skin reaction. Severe local skin reactions reported by Aldara-treated subjects in the pediatric studies included erythema (28%), edema (8%), scabbing/crusting (5%), flaking/scaling (5%), erosion (2%) and weeping/exudate (2%). Systemic absorption of imiquimod across the affected skin of 22 subjects aged 2 to 12 years with extensive MC involving at least 10% of the total body surface area was observed after single and multiple doses at a dosing frequency of 3 applications per week for 4 weeks. The investigator determined the dose applied, either 1, 2 or 3 packets per dose, based on the size of the treatment area and the subject’s weight. The overall median peak serum drug concentrations at the end of week 4 was between 0.26 and 1.06 ng/mL except in a 2-year old female who was administered 2 packets of study drug per dose, had a C_{max} of 9.66 ng/mL after multiple dosing. Children aged 2-5 years received doses of 12.5 mg (one packet) or 25 mg (two packets) of imiquimod and had median multiple-dose peak serum drug levels of approximately 0.2 or 0.5 ng/mL, respectively. Children aged 6-12 years received doses of 12.5 mg, 25 mg, or 37.5 mg (three packets) and had median multiple dose serum drug levels of approximately 0.1, 0.15, or 0.3 ng/mL, respectively. Among the 20 subjects with evaluable laboratory assessments, the median WBC count decreased by 1.4*10⁹/L and the median absolute neutrophil count decreased by 1.42*10⁹/L. **8.5 Geriatric Use** Of the 215 subjects treated with Aldara Cream in the AK clinical studies, 127 subjects (59%) were 65 years and older, while 60 subjects (28%) were 75 years and older. Of the 185 subjects treated with Aldara Cream in the sBCC clinical studies, 65 subjects (35%) were 65 years and older, while 25 subjects (14%) were 75 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. No other clinical experience has identified differences in responses between the elderly and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

10 OVERDOSAGE

Topical overdosing of Aldara Cream could result in an increased incidence of severe local skin reactions and may increase the risk for systemic reactions. The most clinically serious adverse event reported following multiple oral imiquimod doses of >200 mg (equivalent to imiquimod content of >16 packets) was hypotension, which resolved following oral or intravenous fluid administration.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility In an oral (gavage) rat carcinogenicity study, imiquimod was administered to Wistar rats on a 2X/week (up to 6 mg/kg/day) or daily (3 mg/kg/day) dosing schedule for 24 months. No treatment related tumors were noted in the oral rat carcinogenicity study up to the highest doses tested in this study of 6 mg/kg administered 2X/week in female rats (87X MRHD based on weekly AUC comparisons), 4 mg/kg administered 2X/week in male rats (75X MRHD based on weekly AUC comparisons) or 3 mg/kg administered 7X/week to male and female rats (153X MRHD based on weekly AUC comparisons). In a dermal mouse carcinogenicity study, imiquimod cream (up to 5 mg/kg/application imiquimod or 0.3% imiquimod cream) was applied to the backs of mice 3X/week for 24 months. A statistically significant increase in the incidence of liver adenomas and carcinomas was noted in high dose male mice compared to control male mice (251X MRHD based on weekly AUC comparisons). An increased number of skin papillomas was observed in vehicle cream control group animals at the treated site only. The quantitative composition of the vehicle cream used in the dermal mouse carcinogenicity study is the same as the vehicle cream used for Aldara Cream, minus the active moiety (imiquimod). In a 52-week dermal phototoxicity study, the median time to onset of skin tumor formation was decreased in hairless mice following chronic topical dosing (3X/week; 40 weeks of treatment followed by 12 weeks of observation) with concurrent exposure to UV radiation (5 days per week) with the Aldara Cream vehicle alone. No additional effect on tumor development beyond the vehicle effect was noted with the addition of the active ingredient, imiquimod, to the vehicle cream. Imiquimod revealed no evidence of mutagenic or clastogenic potential based on the results of five in vitro genotoxicity tests (Ames assay, mouse lymphoma L5178Y assay, Chinese hamster ovary cell chromosome aberration assay, human lymphocyte chromosome aberration assay and SHE cell transformation assay) and three in vivo genotoxicity tests (rat and hamster bone marrow cytogenetics assay and a mouse dominant lethal test). Daily oral administration of imiquimod to rats, through mating, gestation, parturition and lactation, demonstrated no effects on growth, fertility or reproduction, at doses up to 87X MRHD based on AUC comparisons.

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US38 Rev0407-1
6204 0059 4

Revised: March 2007

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