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## The impact of hormonal treatment on the development of the hip in multiple pregnancy – sonographic assessment\*\*

## Wpływ leczenia hormonalnego na oceniany ultrasonograficznie rozwój stawów biodrowych u dzieci z ciąży wielopłodowych

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### Summary

**Introduction.** An increasing number of multiple pregnancies have been observed within the last twenty years. Multiple pregnancies occur more often in families that have had twins before, or have undergone infertility treatment with hormonal agents to stimulate ovulation. The etiology of DDH – developmental hip dysplasia is multifactorial and is influenced by genetic, hormonal and mechanical factors. Many DDH risk factors occur with greater frequency in multiple pregnancies. The aim of this prospective study was to evaluate the influence of hormonal (gonadotropins, progestogens) treatment on DDH incidence in twins and other multiples.

**Material and methods.** 400 hip joints of 200 newborns were examined ultrasonographically with Graf method. Our sample consists of 166 hip joints of 83 multiples whose mothers had undergone hormonal treatment (Group A) and 234 hip joints of 117 multiples whose mothers had not undergone hormonal treatment (Group B).

**Results.** Group A had 8 Graf Type IIa hips (4.85%), 104 Graf Type Ia hips and 54 Graf Type Ib hips. Group B had 20 Graf Type IIa hips (8.51%), 165 Type Ia hips and 49 Graf Type Ib hips. The incidence of Graf Type IIa was higher in Group B. The difference was statistically significant ( $p < 0.05$ ).

**Conclusions.** Hormonal treatment in a multiple pregnancy cannot be regarded as a risk factor for increased incidence of Graf Type IIa hips.

Key words: developmental dysplasia of the hip, twin, hormonal treatment, ultrasound

### Streszczenie

**Wstęp.** W ostatnich 20 latach obserwuje się narastającą liczbę ciąży wielopłodowych (c.w.). Jako jedną z przyczyn tego zjawiska wymienia się leczenie niepłodności. C.w. występują też częściej w rodzinach, w których wcześniej rodziły się bliźnięta.

Etiologia rozwojowej dysplazji stawów biodrowych (R.D.S.B.) jest złożona. Przyczyny powstania R.D.S.B. podzielono na genetyczne, hormonalne i mechaniczne. Wiele z uznanych czynników ryzyka R.D.S.B. występuje w c.w. ze zwiększoną częstością. Celem pracy było określenie wpływu leczenia hormonalnego (gonadotropiny, progestageny) na częstość występowania R.D.S.B. u dzieci urodzonych z c.w.

**Materiał i metody.** Badaniem objęto grupę 400 stawów biodrowych u 200 noworodków z c.w. Badanie ultrasonograficzne stawów biodrowych wykonywane było metodą Grafa. Badaną grupę „A” stanowiło 166 stawów biodrowych 83 noworodków, których matki przyjmowały preparaty hormonalne. Grupę „B” stanowiły 234 stawy biodrowe u 117 noworodków, których matki nie były leczone hormonalnie.

**Wyniki.** W ocenie ultrasonograficznej wg Grafa w grupie „A” do typu IIa zakwalifikowano 8 stawów biodrowych (4,85%), do typu Ia 104, a do typu Ib 54 stawy. W grupie „B” typ IIa stwierdzono w 20 stawach biodrowych (8,51%), typ Ia w 165, a typ Ib w 49 stawach. Stwierdzono częstsze występowanie stawów biodrowych typu IIa u dzieci z c.w. z grupy „B”. Zależność ta była istotna statystycznie ( $p < 0,05$ ).

**Wnioski.** Leczenie hormonalne w c.w. nie jest czynnikiem ryzyka zwiększonego występowania stawów biodrowych typu IIa.

Słowa kluczowe: rozwojowa dysplazja stawów biodrowych, bliźnięta, leczenie hormonalne, badanie ultrasonograficzne

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## INTRODUCTION

An increasing number of multiple pregnancies have been observed within the last twenty years in the USA, Canada, Japan and the European Union (1-5). However, at the same time the total number of births and the number of spontaneous multiple pregnancies have decreased (5). The factors contributing to this phenomenon, including assisted reproductive technology (ART), hormonal stimulation and hormonal contraceptives, have not been fully elucidated. Assisted reproductive technology (ART) includes: ovarian stimulation, artificial insemination, in vitro fertilization (IVF) and Intracytoplasmic Sperm Injection (ICSI). It is estimated that approx. 15% married couples in Poland undergo infertility treatment (6). In the USA spontaneous multiple pregnancy occurs in 25% of cases, multiple pregnancy following marital infertility treatment – in 75% of cases, including 45% following ovulation induction and 30% following in vitro fertilization (7). It is estimated that there are approx. 125 million multiple pregnancy children with twins constituting approx. 2% of the whole human population of the world (8). Worldwide incidence of twin pregnancy has increased by 50-60%, and that of multiple pregnancy ( $\geq 3$ ) has increased from 310% in France to 696% in the US for 10-15 years (4,5). The incidence of twin delivery in Poland ranges from 1.1% to 1.9% (9).

It is estimated that in developed countries multiple pregnancies following assisted reproductive technology may constitute approx. 30-50% of twin pregnancies and at least 75% of triple pregnancies (4).

Spontaneous dizygotic twin pregnancy most commonly occurs in women at around 35 years of age, multiparas and in women enjoying high socioeconomic status. Higher incidence in older mothers is accounted for by increased level of gonadotropins, particularly of endogenous follicle-stimulating hormone (FSH) responsible for poliovulation (simultaneous development of multiple Graafian follicles in an ovary) (6).

The developmental dysplasia of the hip (DDH) refers to the abnormal formation of this joint, possibly leading to hip dislocation, occurring during intrauterine development, in the perinatal period or within the first postnatal weeks. The etiology of the disorder has a complex nature, with the factors contributing to the deformity of the hip joint development subdivided into hormonal, genetic and mechanical (10)

It is postulated that relaxin plays the most significant role among the hormonal factors (11, 12). Relaxin is a polypeptide whose production is stimulated by increased oestrogen and progesterone levels. It causes the depolymerization of the ground substance of the connective tissue increasing the laxity of capsuloligamentous system. Blood serum relaxin physiologically increases in the third trimester of pregnancy. More relaxin is produced in female than in male fetuses. As relaxin is metabolised in the liver, its increased levels were found in pregnant women and fetuses with liver disorders (13). Oestrogen and progesterone have a

similar, but a less marked direct effect than relaxin (14). Elevated levels of these two hormones were found in the blood serum of newborns with DDH (13, 14).

Until now, however, no authors have presented comprehensive prospective studies based on large samples that would consider how the hormonal treatment of women affects the development of DDH in multiple pregnancy infants. Apparently, it would be advisable to include hormonal treatment in DDH risk factors (14).

The aim of this paper is to verify the association between of female hormonal treatment on the development of hip joints in their multiple pregnancy infants.

## MATERIAL AND METHODS

The study group consisted of infants born in the 2nd Department of Obstetrics and Gynaecology of the Medical University of Warsaw. The study was performed between June 1<sup>st</sup> 2003 and December 2<sup>nd</sup> 2004 in the Department of Neonatology of the Medical University of Warsaw and involved 200 children (400 hip joints) from 95 consecutive multiple pregnancies, including 97 female infants (48.5%) and 103 male infants (51.5%). The study group comprised 172 infants from 86 twin pregnancies, 24 infants from 8 triplet pregnancies and 4 infants from a quadruple pregnancy. The mean duration of a multiple pregnancy was 36 weeks (27 to 41 weeks).

The study did not involve infants diagnosed with neuro-orthopaedic disorders (meningomyelocele), congenital syndromes or those in poor overall condition placed at the ward of intensive newborn care. Only neonates with a birth weight exceeding 1000 g were enrolled (15).

A unified examination protocol was used for all participants. It involved the following elements:

- history taking including medical data concerning as hormonal treatment in the periconceptive and intragestational period in mothers of multiple pregnancy neonates to identify factors potentially increasing the risk of DDH,
- sonographic assessment to morphometrically evaluate hip joint development.

The examination of multiple pregnancy neonates was performed during the first five postnatal days. The clinical and sonographic examinations were carried out by a specialist in orthopedics and traumatology (the first author) with 14 years of professional experience.

The parents received written information concerning the study and gave written consent. Approval from the Local Ethic Committee was assured.

The clinical assessment of multiple pregnancy infants was conducted according to the examination procedure, which included the evaluation of hip joint stability, range of motion, asymmetry of thigh skin folds and coexisting skeletal malformations.

Hip joint sonography was performed according to the Graf method (16) with infants placed in a Graf cradle with their hips flexed at approx. 35° and rotated internally at approx 10°. On the basis of alpha and beta angle values, hip joints were classified into one of 9 groups using a Graf sonometer. The sonographic ex-

amination was performed with a 12.5 MHz linear probe and Ultrasound HDI 3500 device manufactured by Advanced Technologies Laboratories, Bothell, WA, USA.

Statistical analysis was carried out using the Chi-square test. The threshold of statistical significance was assumed at  $p = 0.05$ . The calculations were performed with StatSoft's STATISTICA software package.

## RESULTS

It was stated that hormonal agents were used by mothers of 83 (41.5%) out of 200 multiple pregnancy infants periconceptively and intragestationally. The most common agents used in infertility treatment were gonadotropins (Gonal F, Puregon) for ovulation induction and progestagens (Lutein, Duphaston, Utrogestan) for pregnancy maintenance. Progestagens (Duphaston, Utrogestan, Lutein) had also been used in women with tendency to threatened or habitual abortions.

It was revealed that the prevalence of individual Graf types and intragestational hormonal treatment were significantly correlated (Chi-square test;  $p = 0.029$ ). The prevalence of physiologically immature hip joints (Graf type IIa) was higher in the multiple pregnancy infants whose mothers had not used hormonal treatment. Detailed data are included in table 1. None pathologically dysplastic hip joints were noted during this examination.

Table 1. Graf hip joint type and periconceptive and intragestational hormonal treatment.

Graf hip joint type	Intragestational hormonal treatment		Total
	NO	YES	
Ia	165 70.21%	104 63.03%	269 67.25%
Ib	49 20.94%	54 32.53%	103 25.75%
IIa	20 8.51%	8 4.85%	28 7.00%
Total	234 58.50%	166 41.50%	400 100.0%

Statistically significant relationship (Chi-square test;  $p = 0.029$ ).

## DISCUSSION

It was reported that hormonal agents were used by mothers of 83 (41.5%) out of 200 multiple pregnancy

infants in the periconceptive and intragestational period. The women were administered two groups of hormonal agents: gonadotropins and progestagens.

The agents used in infertility treatment were gonadotropins (Gonal F, Puregon) for ovulation induction and progestagens (Lutein, Duphaston, Utrogestan) for threatened pregnancy maintenance. Progestagens (Duphaston, Utrogestan, Lutein) had also been used in women with tendency to threatened or habitual abortions.

There was a correlation between intragestational hormonal treatment and the prevalence of individual Graf hip joint types in the study group including 400 hip joints of multiple pregnancy infants. The prevalence of physiologically immature hip joints (Type IIa) was higher in the multiple pregnancy infants whose mothers had not been hormonally treated.

The present observations are inconsistent with those of Andren et al. (13) and Wilkinson et al. (14). The study conducted by Wilkinson et al. demonstrated that the effect exerted by both progesterone and oestrogen on the connective tissue is similar to that of relaxin, leading to the depolymerization of the collagen fibres. These hormones have a less marked effect than relaxin. Pisarski et al. (17) stated that the increased tissue elasticity during pregnancy occurs exclusively due to oestrogen, and not gestagen properties. Therefore, the connective tissue of pregnant woman and the foetus becomes more elastic and extendable which numerous authors regard as DDH predisposing factor (13, 18).

Andren et al. (13) reported elevated blood serum oestrogen and oestradiol levels in DDH children.

The present findings do not specify which group of hormonal agents has a more marked influence on hip joint development. This issue needs to be elucidated in a subsequent study.

## CONCLUSIONS

There is a statistical association between the prevalence of individual Graf hip joint types and periconceptive and intragestational hormonal treatment. The prevalence of physiologically immature hip joints (Type IIa) was higher in the multiple pregnancy infants whose mothers had not been hormonally treated.

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