Is the second-born twin at high risk?

M. F. El-Jallad, *MRCOG*; **A. T. Abu-Heija,** *MRCOG*; **S. Ziadeh**[1], *FRCOG*; **A. Obeidat**[1], *MD.*

Department of Obstetrics and Gynecology, [1]Department of Pediatrics, Jordan University of Science and Technology and Princess Badeea Teaching Hospital. Irbid (Jordan)

Summary

Objective: To compare the outcome of the second-born twin with that of the first twin and to find out whether there were any differences and the reason for such differences, if any, and how to improve those differences.

Method: We retrospectively reviewed twin deliveries from the 15th of April, 1994 to the 14th of April, 1996. Excluded were twins weighing <500 gm, either twin with a lethal malformation, and either twin who died before the onset of labour. After this exclusion 246 twin pairs remained in the study. We compared perinatal mortality and 5-minute Apgar scores for both twins.

Results: Perinatal mortality was similar for both twins as well as 5-minute Apgar scores. The twins <1500 gm appeared at special risk. The mode of delivery had no influence on the perinatal outcome of either twin.

Conclusions: The second-born twin may not be at increased risk of complications compared with the first-born twin and caesarean delivery may not improve this outcome.

Key words: Twins; Second twin; Perinatal outcome.

Introduction

The second-born twin is still at some considerable risk compared with the first-born twin despite improvement in perinatology, both with regard to mortality and morbidity.

It was reported from Belgium that perinatal mortality for singletons was 11.3 per 1000, for the first-born twin 35.9 per 1000, and 54.8 per 1000 for the second-born twin [1].

In 1973 Farooqui *et al.* [2], Taylor in 1976 [3], Cetrulo et al. in 1980 [4] and Keslick et al. in 1982 [5] reported advised cesarean delivery for all twin pairs presenting other than vertex-vertex. Chervenak *et al.* [6] in 1984, Laros *et al.* [7] in 1987 reaffirmed this position. But Davidson *et al.* [8] in 1992, Fishmans *et al.* [9] in 1993 and Prins [10] in 1994 challenged the wisdom of this kind of management. All concluded that the second twin is at increased risk, especially for weight <2000 gm, but routine caesarean section for a non-vertex second twin does not appear to improve the outcome.

The present study was conducted at our unit, with modest perinatal facilities, in order to find out whether the second-born twin is at higher risk than the first one and whether the mode of delivery influences perinatal outcome.

Materials and Methods

We reviewed the data of all women who gave birth to twins at the Princess Basma Teaching Hospital (PBTH) from April, 15th 1994 to April, 14th 1996. Excluded from the study were twins weighing <500 gm, either twin with a lethal malformation and when either or both twins died before the onset of labour. After exclusion, 246 twin pairs remained for evaluation and constituted the study group for this retrospective analysis.

Patients were allocated to mode of delivery according to the clinical judgment of the attending obstetrician before or during labour.

The data collected were twin weights, presentation, and delivery method. Measures of neonatal outcome were neonatal death, 1 and 5-minute Apgar scores.

Statistical analyses were performed with the Mann-Whitney or chi-square tests as appropriate. Differences were considered statistically significant when $p<0.05$.

Results

Table 1 shows that the birth weight of twin 2 was slightly lighter, neonatal mortality was similar for both twins, and also there were no differences in 5-minute Apgar scores. In this study there were no intrapartum deaths.

Seven cases of twin 2 neonatal deaths (50%) occurred in newborns weighing <1500 gm compared with 5 cases of twin 1 neonatal deaths (45.5%) occurring in the same weight group who died mainly due to respiratory distress syndrome.

In this study 7 pairs of twins died in the neonatal period.

There were no differences in the neonatal deaths when the presentation of the second-born twin was vertex or nonvertex, and also there were no differences in 5-minute Apgar scores as shown in Table 2.

Table 1. — *Perinatal outcome of twin 1 and twin 2 (n=246)*

	Twin 1	Twin 2	P value
Birth weight (gms)	2441±590**	2392±625	ns*
Neonatal death	11	14	ns
5-minute Apgar score	8.1±1.4	8.01±1.54	ns

ns* = not significant **values are mean ± standard deviation

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Table 2. — *Perinatal outcome in relation to the presentation of the second-born twin*

	Vertex second-born twin (n=153)	Non-vertex second-born twin (n=93)	P value
Birth weight (gms)	2364±603**	2642±532	ns*
Neonatal death	6	8	ns
5 minute Apgar score	8.1±1.5	7.8±1.6	ns

ns*=not significant **values are mean±standard deviation

Table 3. — *Perinatal outcome in relation to the mode of delivery*

	Vaginal delivery (n=176)	Caesarean section (n=70)	P value
Birth weight (gms)			
Twin 1	2362±603**	2644±539	ns*
Twin 2	2362±611	2573±521	ns
Neonatal death			
Twin 1	10	1	ns
Twin 2	10	4	ns
5-minute Apgar score			
Twin 1	8.1±1.5	8.4±1.1	ns
Twin 2	7.9±1.7	8.26±1.06	ns

ns*=not significant **values are mean±standard deviation

Table 4. — *Presentation of both twins (n=246)*

Presentation	No.	%
Vertex-vertex	128	52.02
Vertex-breech	41	16.7
Vertex-transverse	15	6.1
Breech-vertex	27	10.97
Breech-breech	28	11.38
Transverse-transverse	5	2.03
Transverse-vertex	1	0.4
Transverse-breech	1	0.4

When we compared the perinatal outcome of both twins in relation to the mode of delivery (Table 3), we found that although the neonatal deaths were higher in the vaginal delivery group than those delivered abdominally, the differences were not statistically significant.

Table 4 shows the presentation of all twins included in this study. The most common presentation was vertex-vertex (52.02%), followed by vertex-breech (16.7%), breech-breech (11.38%) and breech-vertex in 10.97% of cases.

Discussion

In the present study the overall incidence of twin pregnancy was 13.1 per 1000 deliveries, the neonatal mortality of twin 1 and twin 2 were 44.7 and 56.9 per 1000, respectively.

In this study we compared the second-twin outcome with that of the first twin.

Historically second twins have significantly worse outcomes than first twins, often with mortality rates 30%-50% higher [1-3]. We used the first twin as a control for the second, postulating that the first twin outcome was the best possible for the pregnancy.

No differences in outcome between first and second twin would indicate optimum management of the second twin. Differences in outcomes, on the other hand, would indicate adverse management.

This study is a small one and it may be difficult to draw conclusions. Twin weight appears to be the most important single factor affecting perinatal outcome. All twin 1 neonatal deaths and 93% of twin 2 deaths occurred in those weighing <2500 gm.

However, there were no differences in the perinatal outcome between the two twins in this weight group.

Even non-vertex presentation of the second twin was only marginally associated with adverse outcome.

Second and first twins in these lower weight groups delivered vaginally or by caesarean section, appear to have equally adverse outcomes. Thus, we could not find any factor such as weight, presentation or mode of delivery which appeared to predict outcome differences and nothing else to help us much in making the clinical decision necessary to eliminate adverse outcomes in both twins.

The data suggests that birth order in twin deliveries is not a major factor affecting the outcome and being number two has little negative effect regardless of the weight, presentation or mode of delivery.

Since almost all of the neonatal deaths of both twins occurred in the weight group <2500 gm, mainly due to prematurity and respiratory distress syndrome, reducing this neonatal mortality requires improvement of our perinatal facilities.

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Address reprint requests to:

Dr. S. ZIADEH
P.O. Box 922666, Jabal El-Hussein,
Amman (Jordan)

Intramuscular versus vaginal progesterone in assisted reproduction: a comparative study

M. Perino[1], A. Brigandì[1], F. G. Abate[1], L. Costabile[2], E. Balzano[2], A. Abate[1]

[1]Physiopathology of Human Reproduction, Papardo Hospital, Messina;
[2]2nd Institute of Gynaecology and Obstetrics, University "La Sapienza", Rome - Italy

Summary

The effectiveness and the absorption of two progesterone (P) presentations have been compared for luteal phase support of patients aged ≤ 37 years undergoing an in vitro fertilization (IVF) procedure for the first time, who were stimulated after pituitary desensitization with gonadotrophin releasing hormone agonists (GnRHa). All of them had two ovaries, normal ovarian functions and normal endometrial morphology: the indication for the assisted reproductive technique was the tubal factor. Two hundred and fifty patients were randomly allocated to two groups in order to compare two treatment protocols: Group A: natural i. m. P (50 mg/day, Prontogest, AMSA, Italy); Group B: micronized vaginal P (200 mg/day Esolut, Angelini, Italy). We were able to show that the i. m. P resulted in a higher percentage of pregnancies than the vaginal preparation, with statistically significant differences. We recommend the use of injectable P, and suggest reserving intravaginal P as a second choice for patients who cannot tolerate intramuscular administration.

Introduction

Reproduction in humans involves several steps. In particular, fertilization, implantation and post-implantation embryo development are very important stages for the establishment of a successful pregnancy.

Fertilization is approximately 85% whereas fecundability is only 20% to 25% in women <30 years of age [5]. Thus, implantation appears to be the major limiting step in the reproductive process.

Implantation involves preparation of the endometrium, beginning in the proliferative phase throughout the luteal phase. Progesterone (P) stimulates endometrial gland maturation and decidual transformation of the endometrial stroma, thus providing the essential hormonal support for implantation and the maintenance of the pregnancy [7].

In vitro fertilization - embryo transfer (IVF-ET) techniques could be responsible for luteal phase deficiency (LPD) [10, 11]. In this regard, the prolonged block of pituitary output of luteinizing hormone (LH) could impair the P production by the corpus luteum [13, 24].

The impaired oestradiol (E2) and P production in GnRHa treated cycles could affect endometrial maturation [15, 24, 31]. The necessity of luteal phase support after GnRH/Gn stimulation for IVF has been provided by previous studies [23].

Two possibilities exist for luteal phase supplementation: the administration of human chorionic gonadotrophin (HCG) or P. The use of HCG might yield a higher risk of ovarian hyperstimulation syndrome (OHS) [6]. Natural P supplementation may modulate the negative effect of hyperestrogenism on endometrial maturation [8]. Moreover, P might have an immunosuppressive influence during implantation, thus helping early pregnancy maintenance [12].

In order to "accelerate" endometrial maturation, intramuscular (IM) natural P has also been successfully administered preovulatory [3].

Moreover, it has been demonstrated that the premature luteinization during controlled ovarian hyperstimulation (COH) for IVF-ET has no impact on pregnancy outcome [9].

The use of natural P was also advantageous in preparing artificial cycles in oocyte donation programmes [20, 29], in frozen embryos [19, 26] and blastocysts transfers [16], in 17-α-hydroxylase deficiency syndrome [4], and in persistently retarded endometrium maturation [18].

The aim of this study was to compare the absorption and the effectiveness of two progesterone presentations, an intramuscular administration or a vaginal application, for luteal phase support of patients undergoing an in vitro fertilization procedure.

Materials and Methods

Patients

A total of 300 IVF patients (duration of infertility ≥3 years), undergoing ET for the first time and aged ≤37 years, were randomly allocated to either treatment of this study between November 1994 and July 1997. All of them had two ovaries, normal ovarian functions and normal endometrial morphology. Indication for the assisted reproductive technique was the tubal factor.

Follicular growth stimulation

Pituitary desensitization

All patients were administered GnRHa (Buserelin, Suprefact, Hoechst/UK, Ltd) 400 µg subcutaneously twice a day from day +20 of the previous menstrual cycle until HCG injection (Table 1).

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Multiple follicular growth stimulation

In general, after two weeks of desensitization (17-α-Estradiol plasma levels <30 pg/ml), COH was performed in all patients by administration of follicle stimulating hormone (pFSH, Metrodin 75 HP, Serono, Italy). Follicular growth was then assessed on days +5, +7 and +12 of stimulation by measuring the plasma concentration of oestradiol and by ultrasonographic determinations of follicular size and number. Thus, the dosage of gonadotrophins could be adjusted according to individual response. When serum 17-β-Estradiol concentration exceeded 200 pg/follicle and when at ultrasound at least three follicles had a minimum diameter of 17 mm, ovulation was induced in all patients by IM administration of 10,000 IU of HCG (Profasi, Serono, Italy) (Table 1).

In vitro procedures

Oocytes were retrieved 34-36h after HCG injection under vaginal ultrasound control (day O). IVF Medium (Medi-Cult a/s, Innogenetics, Denmark) was used for culturing. Spermatozoa for insemination were prepared using the swim-up technique. An intra-uterine transfer of pre-embryos at the 2- to 4-cell stage was performed 40-44h post-insemination (day +2). A maximum of four embryos was placed.

Luteal phase support

Starting the day before ET (day +1), patients received luteal phase supplementation until β-HCG evaluation (day +14). Patients were randomly allocated into two groups in order to compare both treatment protocols:

1. Group A (n = 150 ET-cycles): IM administration of 50 mg/day of natural P (Prontogest, AMSA, Italy);
2. Group B (n = 150 ET-cycles): vaginal administration of 200 mg/day of micronized P (Esolut, Angelini, Italy);

On days +1 and +2 after oocyte retrieval, blood samples for 17-β-E2 and P serum levels evaluation, were taken every 2 h for 12 h. Single morning blood samples were also requested on days +7 and +12.

Assays

17-β-E2 and P serum levels were determined by radioimmunoassay (RIA). Intra- and interassay coefficients of variation were 6.5% and 11.5%, respectively for E2. Intra- and interassay coefficients of variation were 6.2% and 10.8%, respectively, for P.

Statistical comparison

Statistical analysis was performed using chi-square test. $P < 0.05$ was assumed as significant.

Results

Patients

Patient characteristics were identical for the two groups. The mean ages were 31.3 ± 3.6 and 31.3 ± 3.0 years, respectively, for groups A and B. The indications for the treatment were similarly distributed in the two groups (Table I).

Ovarian stimulation

There was no significant difference in the dosage of gonadotrophins (16.6 ± 6.7 vs 15.6 ± 6.7 of FSH-ampoules), in the length of treatment (10.5 ± 1.5 vs 10.7 ± 2.0) and in the number of preovulatory follicles (9.7 ± 4.5 vs 9.5 ± 4.6) on the day of HCG administration (Table 1).

Table 1. — *Patients characteristics in the two study groups*

Patient characteristics	Group A *Intramuscular P*	Group B *Vaginal P*
No. of patients	150	150
Days of Gn treatment*	10.5±1.5	10.7±2
FSH Ampoules*	16.6±6.7	15.6±6.7
Follicles ≥ 16 mm ø at HCG*	9.7±4.5	9.5±4.6
Oocytes / Patient*	10.1±5.4	11.5±6.6
Mature Ooctyes	80%	82%
Fertilization Rate	64.7%	66.3%
Cleavage Rate	84.5%	85.8%
Embryos / ET*	3.8±0.9	3.8±1.1

*Values are Means ± SD

Table 2. — *Comparison of results between the two study groups*

Parameters	Group A *Intramuscular P*	Group B *Vaginal P*
No. of ET cycles	150	150
No. of clinical pregnancies/ET	69 (46%)	41 (27.3%)
No. of early abortions/ET	3 (2%)	8 (5.3%)
No. of term pragnancies/ET	66 (44%)	33 (22%)

*Values are Means ± SD

Oocyte retrieval and embryo development

The number of oocytes per transfer cycle (10.1 ± 5.4 vs 11.5 ± 6.6), percentage of mature oocytes (80% vs 82%), fertilization (64.7% vs 66.3%) and cleavage rates (84.5% vs 85.8%) were not significantly different between the two groups. The number of transferred embryos was also similar in both groups (3.8 ± 0.9 vs 3.8 ± 1.1) (Table 1).

Endocrine patterns

Administration of natural IM P resulted in a significant increase from the baseline after 4 h (mean ± SD; 41.9 ± 13 ng/ml; $p<0.01$). Administration of micronized vaginal P resulted in a significant increase from the baseline after 5 h (means ± SD; 39 ± 14 ng/ml; $p<0.01$).

P serum levels with the vaginal P cream were lower in comparison with the IM P administration, but the differences were not statistically significant. In both groups there was a slight but not significant decrease in the control samples.

Overall results

A higher number of clinical (36.4% vs 22.6%) and term pregnancies (30.7% vs 17.9%) appeared in group A, with statistically very significant differences (Table 2).

Discussion

The hypothesis that luteal phase support with exogenous P improves pregnancy rates has been supported by many trials [14, 23, 27, 30]. Nevertheless, it is still not clear what the best route of administration is and whether

it is more advantageous to use P alone or with other compounds [23].

Oral administration involves metabolic inactivation of P during its first liver pass and is frequently associated with drowsiness [22]. Vaginal cream appears to be the most comfortable method for better acceptance [1]. On the other hand, it has been postulated that the vaginal preparation might directly stimulate endometrial production of P-dependent insulin-like growth factor-binding protein-1 (IGFBP-1), which possibly deters embryo implantation [28].

No advantage was found in the addition of oral E2 valerate to IM P luteal phase support of GnRHa/HMG-induced IVF-ET cycles [17]. The combination of vaginal P and HCG resulted in a lower pregnancy rate than the vaginal P alone. It is probably due to a high concentration of E2 related with the role of HCG [21].

The purpose of this study was to compare, separately, the efficacy of the intramuscular P (Group A) and the vaginal cream preparation (Group B) to determine which is more acceptable. The aim was to ensure that a new protocol (B), which could decrease the discomfort of patients, would not affect the well-established overall results obtained with the old protocol (A). Absorption was estimated by measuring P serum levels from blood samples taken at early and midluteal phases. Efficacy was evaluated using the pregnancy and delivery rates per ET. Safety was assessed through specific symptoms and the usual safety monitoring.

Despite previous studies [1] showing that intra- and inter-individual variations in serum P levels were lower after vaginal than after IM administration, we found a significant difference between the two groups (A and B).

Moreover, it has been shown that intravaginal P yields a higher PR than the IM P [25]. However, we found that the percentage of pregnancy/ET was higher in the IM P group, with statistically very significant differences between the two protocols.

No adverse clinical effect was reported by the two groups.

Conclusion

Our study showed that intramuscular natural progesterone results in a higher percentage of pregnancy rate than the vaginal preparation, and the differences are statistically significant.

Considering the benefits associated with patient compliance, the vaginal preparation appears very suitable. On the other hand, it might have an adverse effect on embryo implantation through the direct endometrial stimulation of P-dependent IGFBP-1. This effect could be responsible for the lower PR in the intravaginal than in the intramuscular P group, in spite of the similar P serum levels in the two protocols of this study.

Therefore, we recommend the use of injectable natural progesterone and suggest reserving the intravaginal preparation as a second choice for patients showing high discomfort with the intramuscular administration.

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Address reprint requests to:
LOREDANA COSTABILE
Via Nomentana 531
00141, Rome (Italy)