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Twin Pregnancies Following Induction of Ovulation:
A Literature Review

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A literature review of the occurrence of multiple pregnancies associated with artificial induction of ovulation is reported. This report considers three treatment schedules: (1) clomiphene citrate; (2) human pituitary gonadotrophin with human chorionic gonadotrophin; and (3) human menopausal gonadotrophin with human chorionic gonadotrophin. The majority of the increase in twinning is related to hyperstimulation of the ovary by these medications, resulting in dizygotic twinning. The true incidence of twin pregnancy cannot be calculated because the vital statistics of all nations report live birth rates. Increased rates of fetal wastage, late abortion and prematurity associated with the occurrence of multiple pregnancies are overlooked by these statistics. The increased incidence of twinning appears to be related to the type and dosage of medication used, and the patient's underlying problem.

Key words: Twins, Dizygotic, Ovulation, Induction

INTRODUCTION

A definite increase in the number of multiple pregnancies is associated with artificial induction of ovulation. As early as 1964, an incidence rate ranging between 5% and 16% was reported [35]. Under normal circumstances, twinning occurs spontaneously once in every 89 births, and twin pregnancies can either be monozygotic or dizygotic. The monozygotic twinning rate is constant among different races at 0.3–0.4% [2]. Variable dizygotic twinning rates account for the differences in twinning rates among populations. The rate of spontaneous occurrence of twins ranges from 1.05 to 1.35% [13]. In Ontario, Canada, the rate reported in the 1978 provincial statistics was 1.05% [23].

The two most common side effects of ovulation induction are an increased incidence of hyperstimulation of the ovaries and multiple pregnancies. Multifetal pregnancies appear related to superovulation, and in the case of twins, more frequent dizygotic twinning. Although ovulation induction offers great benefit to women with poor conception and high abortion rates [1,27,30], the side effect of multiple pregnancy may place the patient in jeopardy of higher maternal and perinatal morbidity and higher perinatal mortality. Apparently, the incidence of early abortion in pregnancies where ovulation is induced

does not appear to be larger than normal. On the other hand, pregnancy wastage related to prematurity and late abortion is higher than in spontaneous pregnancy and is closely related to the higher incidence of multiple pregnancies. The incidence of multiple pregnancy using clomiphene citrate appears to be much lower than that of gonadotrophins. The difference may be related to the increased incidence of ovular resportion in clomid-induced gestations compared to gonadotrophin-induced twins [28].

LITERATURE REVIEW

This report contains a review of the literature dating back to 1960 considering three treatment modalities; (1) clomiphene citrate (11 references); (2) human pituitary gonadotrophin (HPG) and human chorionic gonadotrophin (HCG) combination (5 references); and (3) human menopausal gonadotrophin (HMG) and HCG in combination (14 references). These references were generated by a medline search covering the years 1966–1982. The bibliographies of these articles were carefully reviewed to identify further studies as well as to highlight the early reports from 1960 to 1966 which would contribute to an understanding of the association between multiple pregnancy and ovulation induction.

Three main problems interfered with accurate estimates of the frequency of twinning related to ovulation induction.

1. There is a relatively high pregnancy wastage with each method of ovulation induction, and most authors make no attempt to identify multiple pregnancies in this population.
2. Some authors report only pregnancies that have reached viability.

> "These factors present a consistent error in the statistics of pleural gestations for which no exact or even approximate correction can be made. The vital statistics of all nations record only viable births, not total pregnancies. Because spontaneous abortion is more common in multiple pregnancies than in single pregnancies, the incidence of twin pregnancy is greater than the incidence of twin births [13].

Few authors have attempted to report this information.

3. Some authors seem to report on the same patients more than once.

Clomiphene Citrate

Clomiphene citrate is a nonsteroidal oral agent that induces ovulation; its use was reported as early as 1961 [12]. Most authors have used a similar dose range, that is, from 250 mg to 500 mg administered over five days usually from day five to nine of the menstrual cycle. However, many of the early reports cite a variable dosage as high as 1,000–2,000 mg [11,12] of clomiphene/cycle and, in some instances, this was supplemented with 5,000–10,000 U of HCG for resistent cases as well as other medications, such as HMG and prednisone [12,15]. Some authors report poor reproductive success rates in their patients prior to using clomiphene citrate [11,14,34]. Goldfarb reports that, prior to treatment, 160 women had 48 pregnancies, resulting in only nine living babies. Hack similarly reports 44 pregnancies from 86 women with only 13 live births [15].

In assessing the literature regarding the incidence of twinning, some authors report an incidence without the actual number of twin births. It appears that MacGregor [21] and Kistner [20] may be discussing the same population of patients, a collection of data on some 5,000 patients by William S. Merrill Co., the producer and distributor of the medication. The rate of twinning based on these two papers is between 7.8 and 8.9%. Greenblatt [12] also reports an 8% incidence of twinning in 500 cases, although he gives no specific figures in his paper. These data are presented in Table 1.

TABLE 1. Usage of Clomiphene Citrate in Ovulation Induction

Author and year	Regimen	Pregnancies	Abortions	Multiple pregnancies	Twins	Incidence of twins (%)
Vorys (1964)(34)	Variable	9	2	—	—	—
Whitelaw (1964)(35)	Variable	20	—	1	1	5
MacGregor (1968)(21)	50–100 mg ×5	1,744	407	136	—	7.8
Kistner (1971)(20)	50–100 mg ×5	2,042	429	143	—	8.9
Greenblatt (1971)(12)	50–100 mg ×10 / 1,000 mg + 5,000 IU HCG	—	—	—	—	8
Goldfarb (1968)(11)	50–100 ×5 (2,000 mg)	160	17	20	18	11.25
Hack (1972)(15)	50–100 ×5	96	—	—	8	8.3
Evans (1976)(8)	50–100 ×5	65	—	—	—	—
Drake (1978)(6)	50–150 ×5	33	4	0	0	0
Hull (1979)(17)	50–100 ×5	23	5	3	2	8.7
Ruiz-Velasco (1979)(26)	50–150 ×5	109	18	2	2	1.8

Abbreviations: HCG, human chronic gonadotrophin.

Human Pituitary Gonadotrophin

Human pituitary gonadotrophins are obtained from pituitary glands at autopsy. The usual technique includes a protocol where injections of HPG are given sequentially and urinary estrogen and pregnanediol excretion are monitored. The dosage of HPG and the timing of the HCG injection is based on the ovarian response as measured by changes in estrogen and pregnanediol excretion. A single dose of HCG (5,000–24,000 IU) is given to stimulate ovulation of the ripened follicle. An additional injection of HCG is sometimes given during the luteal phase. The results of the literature review are based on five papers. It is possible that Gemzell [9,10] includes patients formerly reported in conjunction with Dr. Roos in 1966 [9].

TABLE 2. Usage of Human Pituitary Gonadotrophin and Human Chorionic Gonadotrophin in Ovulation Induction

Author and year	Regimen	Pregnancies	Abortions	Multiple pregnancies	Twins	Incidence of twins (%)
Crooke (1963)(5)	Individual Dose HPG and 24,000 IU HCG on day 10	10	—	2	—	—
Brown (1969)(3)	Fixed protocol	33	6	8	5	15
Evans (1976)(8)	Fixed protocol	34	6	6	—	—
Gemzell (1978)(10)	Fixed protocol	235	59	54	39	22
Gemzell and Roos (1966)(9)	Fixed protocol	43	11	23	14	32.5

Abbreviations: As in Table 1; HPG, human pituitary gonadotrophin.

The incidence of multifetal and twin pregnancies is significantly higher than the incidence of twinning and multifetal pregnancies using clomiphene citrate. Brown [3] suggests that this increase is related to the dosage of HCG used to induce ovulation. Robertson reports a multiple pregnancy rate of 34% using this method of ovulation induction [25]. He noted that using 5 days of priming with ethinyl estradiol and clomiphene citrate together, followed by the standard HPG–HCG regimen resulted in a multiple pregnancy rate of 8%. He suggested that the use of clomiphene citrate acts as a buffer against the more extreme ovarian response to HPG acting alone.

Gemzell [10] reports the largest series of 235 documented pregnancies and 39 twins. He introduces the term "multiple birth rate," which is the multiple pregnancies at term divided by the total pregnancies minus the abortions. This would not give a true incidence of twinning because the multiple gestations have an increased incidence of second trimester abortion and premature labor with a disproportionately large loss of multiple pregnancies prior to term. This calculation would artifically lower the incidence of multiple pregnancies and twins. These data are presented in Table 2.

Human Menopausal Gonadotrophin

Human menopausal gonadotrophins are more readily available for induction of ovulation from menopausal urine and consequently, are more popular. This review includes 14 references dating from 1968 to 1981. Most authors administer a series of injections of HMG and monitor the ovarian response to urinary or plasma estrogen activity. When a response is noted, a single or multiple injection dose of HCG is administered to stimulate ovulation. These data are presented in Table 3.

Interesting observations were made by some authors regarding multiple pregnancies. Hack [14] reported that 70% of the twins born in this study were female compared with

the expected rate of 49–50% [16]. He also associated hyperstimulation with multiple pregnancy as do other authors [4,7]. Spadoni [31] reports that 25 of 50 patients he was able to follow for two to five years after termination of treatment conceived a total of 36 times. Eighteen of these patients conceived spontaneously without further investigation and/or treatment. Based on this observation, he supports careful use of HMG.

TABLE 3. Usage of Human Menopausal Gonadotrophin and Human Chorionic Gonadotrophin in Ovulation Induction

Author and year	Regimen	Pregnancies	Misc. (%)	Multiple pregnancies	Twins	Incidence of twins (%)
Taymor (1968)(32)	Fixed dosages	20	—	6	—	—
Thompson (1970)(33)	Fixed dosages	299	25	57	43	14.4
Hack (1970)(14)	Individual dosages	78	29	31	23	29.5
Rabau (1971)(24)	Individual dosages	86	29	18	15	17.4
Spadoni (1974)(31)	Individual dosages	26	11.5	8	7	26.9
Ellis (1975)(7)	Individual dosages	43	11.6	13	9	20.9
Wu (1975)(36)	Individual dosages	3	0	2	1	33.3
Jewelewicz (1975)(18)	Individual dosages	89	23	15	9	10.1
Caspi (1976)(4)	Individual dosages	143	21.7	33	23	16.1
Oelsner (1978)(22)	Individual dosages	278	28.1	68	53	25.4
Gemzell (1978)(10)	Fixes protocol	65	22	20	—	—
Hull (1979)(17)	Individual dosages	11	18	4	0	0
Schwartz (1980)(29)	Individual dosages	182	27.5	41	28	15.4
Kemman (1981)(19)	Individual dosages	14	21.4	5	5	35.7

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TABLE 4. Incidence of Abortions and Multiple and Twin Pregnancies Under Various Ovulation Induction Treatments

Treatment	Abortions (%)	Multiple pregnancies (%)	Twins (%)
Clomiphene citrate	21.4	7.4	7
HPG–HCG	23.7	26.2	18.7
HMG–HCG	25.5	25.4	18.4

Abbreviations: As in Table 1 and 2; HMG, human menopausal gonadotrophin.

CONCLUSIONS

In summary, this work reviews the literature from 1960 to 1982 and tries to determine the incidence of twinning from various medical regimes used to induce ovulation. The true incidence of twinning cannot be calculated because of the techniques of reporting vital statistics of all nations which record only live births and not total pregnancies. As noted here, ovulation induction results in an increase in late abortions and prematurity in association with the increased incidence of multiple pregnancy. This factor is not considered by most authors.

The increased incidence of multiple births and twinning appears to relate to several factors. Amenorrheic women require a higher dosage of gonadotrophin and a longer period of therapy with an observed frequency of multiple pregnancy higher than those patients with oligomenorrhea or corpus luteum deficiency. Table 4 summarizes the incidence of abortions, multiple pregnancies, and twins that could be calculated from this review for each of the three major treatment schedules. The observations by Spadoni [31] of spontaneous conception warrant a continued conservative approach to using medication for ovulation induction. This will limit the occurrence of multiple pregnancy and the increased incidence of fetal wastage and prematurity.

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