UTERINE HYPOPLASIA TREATED BY LOCAL INJECTIONS OF OESTROGENIC EMULSION

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Uterine hypoplasia is quite a common condition met with in gynaecological practice and is responsible for a fair number of cases of sterility and infertility. Oestrogenic hormone has been known to have a profound effect on the phase of uterine growth, and the presence of a uterus smaller than normal, whether under-developed or atrophic, is supposed to be an evidence of lack of oestrogenic hormone.

Administration of oestrogens has been shown to stimulate uterine growth in early childhood (Mcphail, 1936, Fred and Soskin, 1937; Evans Varney and Koch, 1940). Several workers have tried to find out the efficacy of oestrogenic hormone administration in uterine hypoplasia but the results have been variable (Moricard, 1936; Foss, 1938, Bourn, 1947; Claubergh, 1934, Mazer and Israel, 1941; Lardaro, 1941). It may be that these differences in results are more due to the mode of administration rather than the direct fault of the hormone, as it can be administered by oral, parenteral or local route.

There are still many glaring gaps in our knowledge regarding the exact mode of action of these hormones, but in view of the increased local vascularity and endocrine receptor theory (Bourne, 1947), the therapy has best chance of success if the required level of hormone concentration is present locally. The local administration of oestrogen by way of application within the uterine cavity or injection within the uterine wall has been of fairly recent origin and the results obtained have been encouraging. It was so thought worth while to evaluate the results of cervical injection of oestrogenic hormone in cases of uterine hypoplasia.

Material and Methods

The present work is based on a study of 50 cases of uterine hypoplasia attending the outpatient department of S. N. Hospital, Lady Lyall and Dufferin Hospital, Agra.

As the interpretation of results of hormonal therapy is difficult on a hetrogenous group, only those cases of uterine hypoplasia were included in this study, in whom the picture

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was not complicated by gross nutritional and menstrual disorders. The absence of malnutrition was judged by clinical and haematological examinations. All the patients selected for study were of normal weight and height and showed complete and convincing signs of sexual maturity as judged by the development of secondary sex characters. After a detailed enquiry, it was confirmed that none suffered from delayed puberty, and their menstrual cycles commenced between the ages of 12 to 16 years (in the majority at 13 years). Furthermore, none of them suffered from any chronic or infective disease for periods varying from 10-15 years prior to reporting themselves for treatment of infertility. Most of them were below 25 years of age, while a few were above this age.

The husbands of these patients were examined prior to treatment, and the various seminal attributes were found to be normal

Control cases: Ten individuals were selected on similar criteria. In these cases the material injected consisted of only the emulsion without the active ingredient. Five injections were given in these cases in the same manner as in the study group, commencing 2-3 days after the cessation of the menstrual period.

A detailed history regarding present complaints, past illness, personal history, diet, gynaecological history pertaining to menarche, menstrual cycle, dysmenorrhoea, vaginal discharge was taken in every case. Every case was subjected to thorough physical examination which included general and systemic examination, and gynaecological examination consisting of general inspection, abdominal palpation, vaginal and speculum examination.

Uterine length was measured in every case with the help of a Meaker's type of hysterometer. The patient was put in the lithotomy position. No anaesthesia or premedication was given. The part was painted with mercurochrome and the Meaker's type of hysterometer was then introduced into the cervical canal after fixing the cervix with a tenacullum under direct vision. It is almost like an uterine sound, with a similar curve, but on its limb there is a measuring slide with a screw attached to it. The portion of the sound which remains outside the vulva has a scale marked in centimeters which reads the length of the uterine cavity or cervical canal when introduced for the purpose. Over this scale, moves the above described slide with a screw fixed to it, whenever the reading has to be noted. At the other end of the slide, there is a circular and bulbous portion which is arrested at the external os of the cervix when the instrument is introduced into the uterine cavity, so the length from the cervix to any point inside the cervix or the uterus is taken accurately. The distance at which obstruction was met with (at the internal os) was noted and the measurement taken at the proximal end of the sliding portion. Then without withdrawing the instrument, for the reading was easy, it was advanced into the uterine cavity until it reached the top of the fundus, when another reading was made. These readings were confirmed by repeating the measurement two or three times. The operation was

performed as gently as possible in order to avoid any trauma to the uterus.

It was necessary to straighten out as far as possible a retroflexed or anteflexed organ for the correct reading to be taken. The following measurements were recorded.

(i) The distance between the external and the internal os.
(ii) The distance between the external os and the fundus.

The first measurement constitutes the length of the cervical canal and has been denoted by the letter C in the formula. The second measurement represents the total length of the cervico-uterine canal and has been denoted by the letter U in the formula for calculation of uterine index as given by Meaker (1940):

$$\text{Uterine index} = \frac{U - C}{C} \times \frac{1}{2}$$

Occasional difficulties were encountered where the hysterometer was caught in one of the crypts of arbor vitae or against the ridge at the level of the internal os.

Method of Administration of the Hormone

One cc. of aqueous suspension containing 10 mg. of oestradiol benzoate was collected in a 10 cc. luer lock syringe, to which was attached a number 18 gauge spinal puncture needle. Cervix was held with a tenaculum and the suspension was deposited in the posterior or lateral lip $\frac{1}{2}''$ to one side of the cervical canal and about $\frac{3}{4}''$ to $1''$ deep in the substance of the cervix. The first and sometimes the second administration of the hormone was incomplete in certain cases which were characterised by the presence of tough and less vascular cervix; the problem, however, resolved itself as the resulting hyperaemia made subsequent deposits easier.

Course of Treatment

The patient was asked to report to the clinic two to three days after the cessation of the next menstrual period. Before the institution of the course of treatment, she was re-examined to confirm the previous findings and change if any in the measurements. The hormone was repeatedly administered in the proliferative phase of several consecutive menstrual cycles. The number of injections in each cycle was only one, its repetition depending on the nature of response of the hypoplastic uterus.

The therapy was discontinued if there was no response after the fifth injection as no further change could be expected in such cases.

Endometrial Biopsy

Endometrial biopsy was carried out in most of the cases before instituting the therapy to exclude any pathology in the uterus and to have a general idea of the condition of the endometrium. This procedure was helpful in excluding cases of endometrial tuberculosis from this study. However, in certain cases, due to the presence of a pin-hole os, endometrial biopsy was not possible as an outdoor procedure.

As a prerequisite to the actual study, total uterine length, length of cervical canal and calculation of uterine index were done in 20 normal healthy women so as to provide

average normal values for these measurements.

Observations

Uterine measurements and uterine index in 20 normal healthy females are given in the following Table I

TABLE 1

	Total length of uterus in cms.	Length of cervical canal cms.	Length of corpus cms.	Uterine index
Range ..	6.3-7.8	2.4-3.1	3.8-5.2	0.75 to 0.916
Mean value ..	7.55	2.29	4.28	0.795

Most of these individuals were between 19 and 25 years of age, while 3 were between 25 and 28 years.

For purposes of demarcation total length below 6.25 cms. and index below 0.75 were considered abnormal and indicative of hypoplasia.

between 21 to 25 years and 10 below 21 years.

The measurements were taken at the onset of therapy and the examination of the patients at this stage also included a record of general impression of the size of uterus ascertained bimanually, appearance and colour of the cervix along with the character of the cervical plug of mucus. Oestradiol injections were given every month 3-4 days after the cessation of the period and measurements taken before that. The

TABLE 2

Results in 10 Control Cases

	Original reading		After last injection		Increase in	Increase in
	Total length	Uterine index	Total length	Uterine index	Total length	Total uterine index
Range	3.8-7.2	0-203	4.0-7.3	0.22 to 0.751	0.1 to 0.2	0.01 to 0.091
Mean value	5.21	0.351	5.71	0.464	0.11	0.032

Of the 50 cases under scrutiny, only four presented with dysmenorrhoea, while in the rest the presenting feature was infertility. After interrogation, menstrual irregularities were revealed in two and amenorrhoea in two others while the rest had normal rhythm. Dysmenorrhoea was present in 16 cases with normal rhythm. All the patients were young, between 17 to 28 years of age, 19 were between 25 and 28 years, 21 patients showed varied response; some improved after two injections, others required three, four or five injections and some did not show any material change even after five injections, and these showing poor response were classed as "failures". The extent of uterine growth also varied from patient to patient.

For purpose of convenience alone the patients were divided into the following categories.

i. Those showing satisfactory response, uterine index at or above 0.75.
ii. Those showing partial response, uterine index between 0.6 to 0.74.
iii. Those showing poor response, uterine index below 0.6.
iv. A fourth category of 8 patients showing variable improvement but in whom the treatment had not concluded and so the results could not be evaluated.

(i) *Satisfactory Response Group*

Out of the total of 42 cases in whom full observations were made, 26 showed good response with 3-5 injections (61.9%). None responded after the first injection. Four showed satisfactory response as judged by the uterine index and increase in total length of the uterus after the second injection. One of these has been included as showing adequate response though the uterine growth hardly improved, chiefly because she conceived after the second injection and aborted later. Thus even in the absence of demonstrable uterine growth with first two injections, the occurrence of pregnancy in a previous infertile woman was taken as evidence of at least clinical improvement, if not morphological. Nine of the patients had normal measurements after the third injection while maximum amount of improvement was noted after the 4th injection in 11 women. Only two, however, improved after the 5th injection (Table 3).

Another point of interest was to observe the relationship of satisfactory improvement with age. It would be apparent from Table 3. that younger patients have a tendency to improve early and perhaps after a fewer number of injections than older ones. Table 4 gives the uterine index and increase in the length of the uterus in the 26 cases showing satisfactory response.

TABLE 3
Satisfactory Response After Number of Injections (Along with Age Factor)

Age (Years)	After 1st injection	After 2nd injection	After 3rd injection	After 4th injection	After 5th injection	Total cases
Below 20 years ..	—	2 (1 + 1)	6	5	—	13
21-25 years ..	—	2	3	4	1	10
Above 25 years ..	—	—	—	2	1	3

TABLE 4

	Uterine index			Total uterine length		
	Original	After last injections	Increase in index	Original	After last injection	Increase in length
Maximum ..	0.648	0.854	0.604	7.6	9.0	2.0
Average ..	0.376	0.769	0.368	5.82	7.4	1.5
Minimum ..	0.236	0.681	0.137	4.5	6.0	0.2

The criterion for satisfactory response was that after treatment the uterine index became 0.75 or above. In two cases the uterine lengths were 7.6 cm. m. and .7 cms. and thus hardly any suggestion of hypoplasia of marked degree, yet the uterine index in these cases was 0.386 and 0.375 respectively. After the injections the lengths in these cases were 7.8 and 7.5 cms. i.e. hardly any significant increase in length occurred in these cases though the uterine index in these cases went up to 0.681 and 0.75 respectively. The significance of these observations will be discussed later.

Partial Response Group

Ten patients showed only partial response even after full trial for five months. Two of these cases were below 20 years of age, 5 between 20 and 25 years, while two were above 25 years of age. Table 5 gives the results in the group.

The increase in uterine index and total uterine length was less marked than in the satisfactory response group.

Poor Response Group

Six patients failed to show any significant increase in uterine index or total uterine length and they constituted the "total failures". Two cases were aged 24 and 25 years while others were above 25 years of age. Results in this group are depicted in Table 6.

The fore-going observations, besides giving a clear impression about good response in 61.9% of cases as judged by significant increase in uterine index, do not bring into prominence the significance of other observations like uterine length, length of cervical canal and length of corpus. An illustrative account of these findings is given in Tables 7(a) 7(b) and 7(c).

TABLE 5

	Uterine index		Increase in uterine index	Total uterine length in cms.		Increase in uterine length
	Original	After last injection		Original	After last injection	
Maximum	0.635	0.704	0.410	7.2	7.8	1.7
Average	0.389	0.624	0.234	5.65	6.49	0.85
Minimum	0.250	0.536	0.069	3.8	4.6	0.5

TABLE 6

	Uterine index		Increase in uterine index	Total uterine length in cms.		Increase in uterine length
	Original	After last injection		Original	After last injection	
Maximum	0.383	0.532	0.187	6.0	6.4	0.6
Average	0.256	0.397	0.140	4.92	5.08	0.41
Minimum	0.207	0.304	0.097	3.8	4.4	0.2

TOTAL 7 (A)

	Total uterine length in cms.											
	3.0 to 3.5	3.6 to 4.0	4.1 to 4.5	4.6 to 5.0	5.1 to 5.5	5.6 to 6.0	6.1 to 6.5	6.6 to 7.0	7.1 to 7.5	7.6 to 8.0	8.1 to 8.5	8.6 to 9.0
Initial	—	3	3	8	3	21	6	3	1	2	—	—
Percentage ..	—	6%	6%	16%	6%	42%	12%	6%	2%	4%	—	—
Final	—	3	3	2	0	3	8	7	11	11	1	1
Percentage ..	—	—	7.15%	4.76%	—	7.15%	19.5%	16.66%	14.28%	26.19%	2.38%	—

TABLE 7 (B)

	Length of the cervix in cms.					
	2.0 to 2.5	2.6 to 3.0	3.1 to 3.5	3.6 to 4.0	4.1 to 4.5	Total No. of cases
Initial	3	16	14	15	2	50
Percentage ..	6%	32%	28%	30%	40%	
Final	6	25	10	1	—	42
Percentage ..	14.28%	59.53%	23.81%	2.38%	—	

TABLE 7 (C)

Length of the Corpus Before and After Treatment

	Length of the corpus in cms.									
	1.0 to 1.5	1.6 to 2.0	2.1 to 2.5	2.6 to 3.0	3.1 to 3.5	3.6 to 4.0	4.1 to 4.5	4.6 to 5.0	5.1 to 5.5	Total No. of cases
Initial	5	12	13	14	6	—	—	—	—	50
Percentage ..	10%	24%	26%	28%	12%	—	—	—	—	
Final	—	3	2	2	2	8	15	8	2	42
Percentage ..	—	7.15%	4.76%	4.76%	19.05%	19.05%	35.71%	19.05%	4.76%	

The initial uterine length in 42% of cases was between 5.6 and 6 cms. while 34% had lengths between 3.6 and 5.5 cms. and only 24% between 6.1 and 8.0 cms. After treatment uterine length varied mostly in the range 6.1 to 8 cms. From Table 7 (b) it is clear that after treatment the measurements revealed a definite shortening of the cervical canal, which in association with an increase in the total uterine length was responsible for higher uterine index after treatment. The measurements of the body of the uterus ran reverse to those of cervical length (Table 7C). Thus while the body of uterus measured between 1.6 to 2.5 cm. in 25 patients, the length in this range was found only in 5 patients after treatment. Similarly, after treatment there were 31 patients (73.8%) in the range of 3.6 to 5 cms. when not one patient had body of uterus measuring above 3.5 cms. before treatment was started. Calculation of uterine index in different ranges was informative. Post-therapy uterine index carried between 0.66 to 0.91 in 29 patients while in the same range there was no patient before the treatment was instituted.

Other Observations

i. There was no change in the position of the uterus after oestrogen therapy and the number of anteflexed and retroflexed uteri remained the same.

ii. During treatment with oestrogen there was significant increase in vascularity of the cervix in patients who showed satisfactory response, whereas no change was seen in those who failed to respond. In addition these cases showed a definite thickening of the cervix which in many instances differed dramatically from the narrow conical and pale appearance of the hypoplastic organ.

iii. Three cases, two from satisfactory response group and one from partial response group, developed cervical erosion.

iv. Cervical plug of mucus, in most of the cases who responded, became thin, watery, while no such change was seen in poor response group.

Endometrial Biopsy

Endometrial biopsy was possible in 32 cases. The histological diagnosis, alongwith the type of response is shown Table 8.

TABLE 8

Showing Endometrial Pattern in 32 Patients

S. No.	Histological diagnosis	No. of cases	Type of response		
			Satisfactory	Partial	Poor
1.	Proliferative phase	11	6	4	1
2.	Proliferative with tendency to dilatation of glands	1	—	1	—
3.	Early secretry phase	5	5	—	—
4.	Late secretory phase	15	15	—	—

It would be apparent that all cases with secretory endometrium responded well to therapy, while of the 11 patients with proliferative endometrium, such a response occurred in 6 cases, partial response in 4 cases and total failure in one case.

Discussion

An estimate of the degree of hypoplasia made on the basis of bimanual examination may very often be misleading, and majority of the workers in the field have based their studies on the measurement of uterine length. Meaker (1940, 1954) and Meigs (1939) have emphasized the importance of comparing the length of the corpus and cervix and using this resultant uterine index as an indication of uterine development

In the present study uterine index was calculated regularly and 50 cases of uterine hypoplasia were followed up with repeated measurements for a period extending from two to four months. Normal values of the size of the uterus were arrived at by measurements in 20 healthy normal, nulliparous women. In the 10 cases of uterine hypoplasia who were given bland intracervical injections for a period of five months, there was no significant alteration either in the size of uterus or the uterine index. Such a control was necessary to rule out the possibility of local irritation playing any part in the therapy. The size of the uterus in healthy women so analysed provided the standard values of study. A uterine index of above 0.75 was considered normal and values below this were thought pointing towards hypoplasia. Similarly length of uterine cavity below 6.2 cm. was taken as a criterion of a small uterus.

Jeffcoate and Lever (1945) dispute the value of uterine index on the ground that low values indicating hypoplasia would be obtained whenever cervical canal is unusually long irrespective of the size and development of the body of the uterus. Agreeing with this, reliance was not placed on uterine index in cases of long cervical canal. However, in two of such cases uterine index rose from 0.375 to 0.750 after the therapy without any material increase in total uterine length. This can be considered as an indirect evidence of past uterine hypoplasia and uterus in patients of this type can be called "infantile type".

Assessment of total uterine length in addition to uterine index is certainly a helpful criterion upon which results can be based. In most instances or at least in all showing satisfactory response, increase in total uterine length runs parallel to increase in uterine index.

The overall results in our series as judged by the increase in total uterine length and index was satisfactory. Leaving six patients who failed to show any improvement even after five injections, all others improved to some extent or other. Thus in 61.9% of cases uterus returned to normal size, in 20% the increase, though not up to the mark, was still significant, and the remaining 16% who were still under treatment when final observations were made, showed partial response to therapy. In 10 cases response was considered partial or incomplete because even after the completion of the course of five in-

jections the response was not complete. But this does not mean that further increase in uterine index or length would not occur with prolonged treatment. Indeed, this type of occurrence has been emphasized by Tur *et al.* (1949).

Apparently, therefore, the value of locally administered oestrogens cannot be disputed. Sarafield (1955) reported satisfactory response in all his 30 cases of uterine hypoplasia with proved secretory endometrium by locally administered oestrogens. Karande *et al.* (1959) on the contrary, found that effect of locally administered oestrogen was only temporary and there was a wearing away of the effects within 20 days i.e. till just before the next withdrawal bleeding. Mazer and Israel (1941) also considered the effect of local oestrogens only a temporary phenomenon. Further follow up of our cases for some months would have enabled us to verify the validity of this statement. However, in the few cases which we have followed there was a tendency towards decrease in both the total uterine length as well as uterine index when the treatment was stopped.

Age of the patients appears to be an important factor in deciding response to therapy. The patients who were relatively young had an overall better response than those who were slightly older. Meaker (1954) had suggested that the uterus loses its response after 20 years of age. This concept has been critically challenged by various workers and our observations also are contrary to this concept and we can only say that chances of successful therapy decrease with advancing age.

In this series there were 5 atypical cases with long cervical canals and normal total uterine lengths. On the basis of low uterine index and small size of the corpus, these were included amongst cases of hypoplasia which ultimately proved correct in view of response to treatment. In all these cases there was a reduction in the length of cervix by 1-1.5 cm. The shortening of cervix was observed not only in these cases but in all cases of the series who showed some response to treatment. We have no explanation to offer for the shortening of cervical canal but we wonder if this is not similar to the shortening of the cervix which is constantly observed as a normal infantile uterus attains growth and maturity.

Reversion of cervical plug of mucous to normal consistancy is another feature of treatment and can be considered an indication of adequate response. Studies on the crystallization phenomenon of the cervical mucus (Karande *et al.* 1959) have been used as a rough measure of blood oestrogen activity in cases of hypoplasia.

The ultimate value of oestrogens in the treatment of hypoplasia is difficult to estimate. In all our patients with secretory endometrium, the uterus attained normal size while satisfactory response was noticed in only 50% of cases with anovulatory cycle and proliferative endometrium. It is tempting to assume that patients with ovulatory cycles are perhaps best suited for oestrogen therapy. Sarafield (1955) observed satisfactory response in all his cases with secretory endometrium and as many as

50% of his cases conceived after the treatment.

Summary

The present study consists of evaluation of intracervical injections of oestrogenic hormone in the treatment of uterine hypoplasia. As a result of measurement of total uterine length, cervical canal and calculation of resultant uterine index in 20 normals and 60 patients of uterine hypoplasia, ten of whom acted as controls, a critical evaluation of the use of these measurements as criteria of the uterine growth, has been made.

The average normal length of the uterus was found to be 7.55 cm. that of cervical canal 2.29 cm. and uterine index was 0.795. The uterus was considered to be hypoplasic when the total length was below 6.25 cm. and index lower than 0.75. Of the 50 patients so studied with intracervical injections of oestrogenic hormone given for a period extending from 2 to 5 months, 26 showed satisfactory response with return of uterus to normal size, ten improved partially, while 6 were resistant to treatment; 8 patients were still under treatment when results were compiled and had all shown partial improvement. The patients who were relatively young showed an overall better response than those who were relatively older.

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