

CRITICAL REVIEW.

Exophthalmic Goitre and Pregnancy, Labour and the Puerperium.

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At the present time it is difficult to obtain any definite information on this subject, the statements in the standard text-books and monographs are meagre and frequently contradictory. An attempt is therefore made here to collect a few of the statements that have been made on the subject to enable conclusions to be drawn.

There would appear to be no sharp line of demarcation between a simple and an exophthalmic goitre (Graves' disease); the symptoms of the latter may appear when a patient has had a simple goitre for years, or exophthalmic symptoms may be present with little obvious thyroid change.

The subject falls into three divisions—(1) the influence of child-bearing on the goitre; (2) the influence of goitre on child-bearing; (3) the condition of the child born of exophthalmic mothers.

The influence of Child-bearing on Exophthalmic Goitre. All writers seem to agree that swelling of the thyroid is common during pregnancy, and that the swelling may persist after delivery. Aetius,¹ in 1567, suggested that a bronchocele was caused by straining, and gave parturition as an example. Guillemeau,¹ in 1612, noted the connection between goitre and pregnancy. More recently an attempt has been made to correlate the thyroid enlargement with the efforts of the patient to combat the toxæmia of pregnancy. Nicholson² strongly holds this view, and Lange³ found that only 25 out of 133 women examined during the last three months of pregnancy had *not* got hypertrophied thyroids, and of these 25 no less than 18 had severe albuminuria. There is, however, evidence that symptoms of the toxæmia of pregnancy are common with Graves' disease.

Taking now cases with the classical symptoms of Graves' disease, one finds that Whitridge Williams⁴ is almost alone in stating that pregnancy plays no part in the production of Graves' disease; most other standard text-books make opposite statements; for example, Hirst⁵ says that it may originate during pregnancy, but will usually

disappear after delivery. He mentions a case where the disease recurred in three successive pregnancies—the patient being well at other times. Edgar states that a small minority are improved, but a great majority made worse; it may appear in the *puerperium* of successive pregnancies. Garrigues⁷ agrees that patients get worse during pregnancy. Wilson⁸ saw a patient where exophthalmic goitre appeared in the third pregnancy.

Halliday Croom criticises Bucquet's⁹ article, and excludes many of his cases, but accepts the fact that in two cases the pregnancy added exophthalmic symptoms to a pre-existing simple goitre. Croom's¹⁰ own twelve private cases were all made temporarily worse by the labour. Jouin¹¹ states that Graves' disease has intimate relation with pathological conditions of the pelvic organs, and quotes 43 cases (mostly gynæcological). Many of his cases appear to have been very slight ones, and hardly worth the name of exophthalmic goitre. Doleris¹² disagrees with Jouin, and thinks that fully-developed Graves' disease is, on the whole, rare in patients with pelvic lesions. Freund¹³ had a patient who had a simple goitre in her first pregnancy, which disappeared five weeks after labour; in the third pregnancy Graves' disease appeared, but all symptoms, except slight tachycardia, had gone three days after delivery. This disappearance of symptoms is much more rapid than in other recorded cases. Mackenzie¹⁴ states that in several instances he has seen great improvement or even recovery result from pregnancy.

Dr. Harold Pretty gives me details of a case remarkable on account of the severity of the Graves' disease. The first symptoms occurred in 1907, two months after marriage, and rapidly increased to an alarming extent, the vomiting being especially marked. Improvement took place till 1908, when she became pregnant for the first time; within three months the patient was desperately ill with acute Graves' disease, but the symptoms lessened during the ensuing six weeks, and she was delivered at full term of a normal child. The labour was normal, and the child has remained healthy. The improvement was maintained till 1910, when a second pregnancy occurred, and again the patient was in grave danger from vomiting and general exophthalmic symptoms. Improvement occurred when the pregnancy had gone to four and a half months, and two months later she was able to leave her bed. A normal premature labour occurred. The foetus was normal. Puerperium uneventful.

I have recently seen two cases where the symptoms rapidly increased during early pregnancy, but subsided before delivery. In both cases labour was uneventful (forceps used in one case owing to cyanosis). No excessive post partum hæmorrhage took place. In one case the child was normal. The other child showed abnormalities, which I hope to describe subsequently.

Several cases have been published where symptoms of Graves'

disease have accompanied the ordinary symptoms of the toxæmia of pregnancy. This is at first sight all against Nicholson's work on the toxæmia of pregnancy being due to deficient thyroid activity, as exophthalmic goitre is usually regarded as due to over-activity of the gland, and all the classical symptoms can be produced by an overdose of the gland substance by the mouth in dogs and monkeys. But it must be remembered that myxœdema fairly frequently accompanies or terminates Graves' disease, and myxœdema is certainly due to a deficiency of the thyroid secretion. It is only necessary just to mention that the most recent research points to the parathyroid glands, and not the thyroid, being of paramount importance in these conditions.

As examples of the onset or increase of exophthalmic goitre with the toxæmia of pregnancy may be quoted Audebert's¹⁵ case—a patient with œdema and signs of toxæmia who developed Graves' disease when seven months pregnant. The toxæmia increased, and she was comatose when delivered. By four months later gradual improvement of the Graves' disease had occurred. He quotes many other toxic states (*e.g.*, syphilis and typhoid fever), which have been credited with the causation of Graves' disease. Stowe¹⁶ gives details of a patient with Graves' disease of some two years' standing, who became pregnant on October 8 1907. Incessant vomiting occurred, and the exophthalmic symptoms became very severe. The urine contained 2 per cent. albumen, no sugar. The uterus was emptied on December 28th under ether anæsthesia, but the patient died six days later. One of Halliday Croom's cases died of eclampsia. Skutsch¹⁷ had a patient who had exophthalmic symptoms during her first pregnancy; the second and third were normal, but severe symptoms of exophthalmic goitre appeared in the fourth. Labour was induced and dead twins delivered, but the patient died in coma soon after. The changes in the liver in cases of the toxæmia of pregnancy are well known, and Pottet and Kervilly¹⁸ have described changes in the thyroid in cases of eclampsia; it must be added that microscopic alterations in the thyroid have been described in many subacute hepatic diseases.¹⁹

The influence of Exophthalmic Goitre on Child-bearing. There can be little doubt that Graves' disease strongly predisposes to sterility, for, although the disease typically occurs at the very age when pregnancy is most common, yet pregnancy in patients with pre-existing Graves' disease is rare. Halliday Croom knew of only one patient with a goitre among 15,000 cases in the Edinburgh Maternity Hospital, and this patient does not seem to have had exophthalmos. Martin²⁰ saw no example among the patients that he examined. The Queen Charlotte's Hospital Reports for 1907–8–9 mention no case.

This sterility may be due to the fact that the uterus and ovaries tend to atrophy, and that amenorrhœa is frequently present.²¹ The

breasts may also atrophy, and so may the labia majora and mons veneris.²² Cheadle,²³ in 1878, had noted this. The atrophy may be quite rapid, as Hodemaker²⁴ recorded a case in a girl of 29 with exophthalmic goitre of only two years' standing.

This atrophy does not necessarily cause absolute sterility, as Theilhaber²⁵ gives an example of a patient who became pregnant after long-standing amenorrhœa. The influence of Graves' disease on menstruation seems very variable. Russell Reynolds²⁶ found menstruation normal in 46 out of 49 patients. If the patient becomes pregnant ante-partum hæmorrhage is said to be frequent, Lawson Tait²⁷ being quoted as the authority. Many of the recorded cases have ended in abortion or premature labour, but an important point which a study of the labours of these patients brings out is the frequency of post partum hæmorrhage. Halliday Croom had 12 cases of labour, with Graves' disease, in private practice; eight were normal. Of the other four, one had severe post partum hæmorrhage, and super-involution followed; the second had accidental hæmorrhage; the third miscarried at the third month, post partum hæmorrhage was very severe and super-involution followed; the four had a normal labour, but died of post partum eclampsia. Mackenzie's patients had post partum hæmorrhage. Nicholson²⁸ attended two cases; hæmorrhage was severe in both. He also noted that the secretion of milk was unusually free; in this connection it may be added that thyroid given to a lactating woman is said to increase the flow of milk;²⁹ but in opposition to this normal lactation may occur after total thyroidectomy. Bang³⁰ states that the active principle is excreted by the milk.

Mossé and Cathala³¹ report an interesting case where a marasmic goitrous child improved rapidly when thyroid was administered to its wet nurse. Bramwell³² noted symptoms of hyperthyroidism in a child each time that thyroid extract was given to its mother, who was suffering from Graves' disease which had come on during the pregnancy. In Audebert's case (*loc. cit.*), which was breast-fed, there is no mention of the child being affected. In one case recently under observation I was unable to notice any increase in the pulse-rate in a normal child which was fed on the milk from an exophthalmic mother for over 24 hours.

The condition of the Fœtus born of Exophthalmic Mothers. The state of the fœtus, and especially the condition of its thyroid gland, has been usually omitted from the published description of cases. This may be due to some doubt as to what is the normal condition of the thyroid in the fœtus. As a rule it does not seem to be functional at birth. Berry³³ states that it is almost solid and contains little colloid. Ballantyne³⁴ points out that it cannot contain iodine, but after the third month of intrauterine life thyro-mucin is present; the reappearance of this substance in adult life

has been regarded as a cause of exophthalmic goitre.³⁵ Ballantyne quotes Svehla,³⁶ who states that the foetal thyroid does not contain any substance to accelerate the pulse. The former suggests that if the maternal thyroid is deficient the foetal gland may assume its post-natal function.

Ochsner and Thompson³⁷ state that the hyperplasia produced by a partial thyroidectomy may be reduced to colloid by giving iodine. It would thus appear that one of the essential differences between the foetal and adult thyroid is the presence of iodine in the latter. That the maternal gland has some influence on the foetus *in utero* is proved by the experiment of Edmunds,³⁸ who removed the whole thyroid and one parathyroid from a pregnant bitch. Four months later it gave birth to a puppy with a hypertrophied thyroid with absence of colloid. Edmunds was confirming Halstead's work. Graves' disease (hereditary or otherwise) is extremely rare in infancy. Berry (*loc. cit.*, p. 176) says it is "almost, if not quite, unknown before the age of two and a half years." Ochsner and Thompson show a photograph of a five months old child with Graves' disease. The disease was present five weeks after birth. It was the fourth child and was a month premature. The mother herself suffered from Graves' disease, which had come on during her first pregnancy. Reference is given to another case in infancy by Loddo.⁴⁰

T. Graves, in 1910, showed at a Laboratory Meeting of the Pathological Section of the Royal Society of Medicine, a litter of six bull-terriers, all of which had all the classical symptoms of exophthalmic goitre well marked at four weeks old, when he first examined them. The mother was a normal bitch.

Many cases are on record of the disease appearing about the age of puberty in several members of the same family. Rosenberg⁴¹ saw it in one sister, father, two paternal aunts and the paternal grandmother of a patient; and Mackenzie⁴² mentions a hysterical mother of ten children, where eight out of the ten had exophthalmic goitre in varying degrees, and one daughter had four grandchildren affected.

Regarding the after-histories of the children born of mothers with exophthalmic goitre little is recorded. Church⁴³ delivered an exophthalmic mother of twins; one died, the other was an epileptic when 15 years of age (there was a family history of epilepsy). Dr. F. J. Poynton gives me details of a rare case recently under his observation. A girl developed Graves' disease at 18, with much exophthalmos and thyroid enlargement. She married at 25; a year later a child was born. At this time the mother's symptoms were well marked, but they improved after delivery except some tachycardia which persisted. The child, when four months old, was a typical cretin. She improved under thyroid medication, and is now a healthy child of five years. In Pretty's case, as mentioned above, the infant is quite healthy after 2½ years.

Conclusions. The results published are so contradictory that doubts are raised whether true Graves' disease has been present in all cases. Where Graves' disease was undoubtedly present it would appear that sterility is common. If pregnancy takes place premature labour and ante-partum hæmorrhage occasionally occur. Severe post partum hæmorrhage has been sufficiently frequent to make it an important complication. Super-involution with amenorrhœa certainly takes place, but only in a small proportion of cases, as repeated pregnancies are frequently seen.

Regarding the connection between Graves' disease and the toxæmia of pregnancy, it is necessary to note how nearly all the symptoms and signs of toxæmia may be present in an exophthalmic patient who is not pregnant. Œdema, for instance, is not infrequent, and usually affects the feet and eyelids. Vomiting unrelated to the ingestion of food is common and may become a grave symptom; even epigastric pain is sometimes present, and diacetic acid and acetone have been found in the urine. Albuminuria does occur, but is somewhat rare. Relapses and recurrent attacks of Graves' disease have been described comparable to the cases mentioned where a patient only suffers during her pregnancy or puerperium. It would thus appear that the normal symptoms of exophthalmic goitre (frequently made worse by the occurrence of gestation) have been mistaken for the toxæmia of pregnancy, but no true relation of the two conditions has been proved to exist. Treatment in these cases should be directed towards the exophthalmic goitre and not towards a hypothetical toxæmia.

Pregnancy is an important factor in the ætiology of the disease, and on the whole makes it worse. The patients may pull up lost ground towards the end of the pregnancy, but are again made worse by the labour in a good many instances. Improvement during the puerperium is usual and occasionally even a cure may take place. Relapses during subsequent pregnancies are to be expected.

The risks to the mother are not so great as to contra-indicate marriage.

The fœtus is usually normal and healthy; abnormalities present at birth are probably coincidences. The amount of evidence obtainable regarding the effect of lactation is too small to draw conclusions from, but no proof has been given that breast-feeding is dangerous to the child.

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