Gastrointestinal Insulinotropic Hormones in Normal and Gestational-Diabetic Pregnancy

Response to Oral Glucose

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SUMMARY

The responses of gastric inhibitory polypeptide (GIP), gut glucagon-like-immunoreactivity (gut GLI), insulin, and pancreatic glucagon to a 50-g oral glucose load were studied in late pregnancy and postpartum in 11 normal women, 10 normal weight gestational diabetics, and 10 overweight gestational diabetics. The GIP response to glucose was impaired in pregnancy in all three groups. In pregnancy, the GIP response was smaller in both groups of gestational diabetics than in normal women, whereas postpartum, the GIP response was lower than normal in the normal weight gestational diabetics only. In pregnancy, the gut GLI response to glucose was reduced in the overweight gestational diabetics and abolished in the normal women. The insulin response to glucose was increased in pregnancy in all three groups. Moreover, it was higher in the overweight gestational diabetics than in the other two groups in pregnancy and postpartum. In the normals, the suppression of glucagon levels after glucose ingestion was more marked in pregnancy than postpartum, whereas no such effect was seen in gestational-diabetic pregnancy. It is concluded that pregnancy—normal as well as gestational-diabetic—is accompanied by profound changes in the secretion of gastrointestinal insulinotropic hormones after glucose ingestion. These findings may be important for the understanding of changes in metabolism and gastrointestinal physiology in gestation.

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During pregnancy glucose tolerance is significantly impaired in normal women,[1] and in approximately 1% of all pregnant women the glucose tolerance becomes diabetic.[1] In these gestational diabetics, glucose tolerance is most often normalized postpartum, but the patients have an increased risk of developing overt diabetes later.[2] Neither the reason for the diabetogenicity of pregnancy nor the pathophysiologic mechanism behind the development of gestational diabetes has been completely clarified, but both are believed to be multifactorial.[3] Normal pregnancy is accompanied by peripheral insulin resistance, as demonstrated by a decreased blood glucose response to i.v. administered insulin,[4,5] a finding that may be related to the reduced number of insulin receptors in this state.[6] Possibly to overcome this restraint, prevailing insulin levels are increased in gestation.[3] In vitro[7–9] and in vivo[10] studies have indicated that the hyperinsulinemia of pregnancy may be due to increased β-cell sensitivity to glucose in pregnancy, as well as to increased β-cell mass in this state.[11,12]

In pregnancy, insulin secretion is, however, not sufficiently increased to maintain normal glucose tolerance. This may partly be explained by the decrease of gastrointestinal potentiation of insulin secretion after oral glucose ingestion in pregnancy.[13] Thus, unaltered gastrointestinal stimulation might bring about more insulin and thereby improve glucose tolerance.

The most important gastrointestinal insulinotropic hormone is gastric inhibitory polypeptide (GIP),[14] but gut hormones with glucagon-like-immunoreactivity (gut GLI) may also be capable of stimulating insulin secretion.[15] We have previously found a diminished GIP response to oral glucose in normal pregnancy[16] and the present investigation was undertaken to compare the GIP and gut GLI responses to oral glucose in pregnancy and postpartum in normal women and in women with gestational diabetes. Two groups of gestational diabetics were studied, one consisting of normal weight and the other of overweight individuals.

MATERIALS AND METHODS

Subjects. One study group consisted of 11 normal female volunteers, all of whom had normal glucose tolerance. None had a family history of diabetes, had glycosuria, or received

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TABLE 1
Pertinent clinical data

	Normal women	Gestational diabetics		Difference between groups:		
		Normal wt	Overweight	1 and 2	2 and 3	1 and 3
	Group 1	Groups 2	Group 3	P <	P <	P <
N	11	10	10			
Age (yr)	25 ± 1*	31 ± 2	31 ± 1	0.01	NS	0.01
H (cm)	169 ± 1	165 ± 2	164 ± 3	NS	NS	NS
Prepregnancy body wt (kg)	58 ± 1	60 ± 2	82 ± 3	NS	0.01	0.01
Wt gain in pregnancy (kg)	11 ± 1	13 ± 3	10 ± 2	NS	NS	NS
Birth wt of infant (g)	3281 ± 80	3470 ± 178	3394 ± 109	NS	NS	NS
Time of investigation						
in pregnancy (wk)	38 ± 1	35 ± 1	34 ± 1	NS	NS	0.01
postpartum (wk)	11 ± 1	6 ± 2	8 ± 2	NS	NS	NS

* Mean ± SEM.

diuretics or any other drugs during pregnancy. Pertinent clinical data are given in Table 1.

The gestational diabetics were detected by the department's routine screening procedure for diabetes in pregnancy.[1] The procedure includes a 50-g oral glucose tolerance test, which is considered abnormal if two or more plasma glucose determinations exceed the mean + 3 SD curve pertaining to a group of 46 normal nonpregnant controls investigated by exactly the same procedure.[17] These diagnostic criteria correspond closely to those advocated by the National Diabetes Data Group.[18] None of the patients required insulin or oral hypoglycemic drugs. Postpartum, all had a normal glucose tolerance test. In pregnancy, the gestational diabetics were studied at the time of diagnosis before diet had been recommended. Diet was discontinued after delivery. Two groups of gestational diabetics were studied, one consisting of 10 normal weight individuals and the other consisting of 10 women more than 10% overweight before pregnancy. Relevant clinical data are given in Table 1. Informed consent was obtained from all persons.

Investigative procedure. All women were investigated in late pregnancy and postpartum and served, thus, as their own nonpregnant controls. For at least 3 days before the investigations, all women ate at least 2000 kcal including 300 g of carbohydrate each day. The tests were performed in the morning after overnight fast and abstinence from smoking. Immediately after arrival, a cannula was inserted into an antecubital vein and a 20-min rest was allowed before the onset of blood sampling. At 0 min, 50 g of glucose in 200 ml of water was given orally. Blood samples were drawn at −10, −5, 15, 30, 45, 60, 90, 120, 150, and 180 min into chilled heparin tubes containing 500 KIU Trasylol/ml. Within 30 min, the samples were centrifuged at 4°C and plasma stored at −25°C until assayed.

Laboratory analyses. Plasma was assayed for glucose by a glucose dehydrogenase method[19] and by radioimmunoassays for GIP,[20] gut GLI,[21] insulin,[17] and glucagon.[22] All samples from one person were run in the same assay to minimize errors due to interassay variation. All peptides investigated are stable in frozen plasma for periods relevant to the present investigation.

Statistical analyses. Data are presented as mean ± SEM. The significance of difference between means within the groups of patients was tested by Student's *t* test for paired observations. Differences between the three groups were first tested by one-way analysis of variance. When this procedure showed variation to be present, further analysis was performed by Student's *t* test for unpaired observations. Differences resulting in P values below 0.05 were considered significant.

The integrated hormone responses were calculated by integration of the hormone concentration curves from 0 to 180 min using fasting levels as baselines.

RESULTS

Fasting concentrations. Table 2 gives the fasting concentrations of glucose, GIP, gut GLI, insulin, and glucagon in the three groups in pregnancy and postpartum.

Fasting plasma glucose was reduced in pregnancy in the normal women but not in the gestational diabetics. In pregnancy, fasting glucose levels were higher in both groups of gestational diabetics than in normal women, whereas postpartum, only the overweight gestational diabetics had elevated fasting plasma glucose.

No variation of fasting plasma GIP concentrations was observed within or between the groups.

Postpartum, fasting plasma gut GLI in the normal women was higher than in pregnancy and also higher than postpartum findings in the gestational diabetics. In the gestational diabetics, fasting plasma gut GLI levels were not influenced by pregnancy.

In all three groups insulin levels after an overnight fast were higher in pregnancy than postpartum. Moreover, in pregnancy levels were significantly higher in the normal weight gestational diabetics than in normal women, and even higher in the overweight gestational diabetics. Postpartum, the overweight gestational diabetics still showed elevated fasting plasma insulin concentrations after overnight fast.

Fasting plasma glucagon was increased in pregnancy in all groups but no difference between the groups was observed.

Plasma concentrations after glucose ingestion. Figure 1 shows the concentrations of glucose, GIP, gut GLI, insulin, and glucagon in pregnancy and postpartum in the normal women. Figure 2 shows the corresponding findings in the group of normal weight gestational diabetics and Figure 3, the findings in the overweight gestational diabetics.

In all three groups of patients plasma glucose concentrations after oral glucose were higher in pregnancy than post-

TABLE 2
Fasting plasma concentrations of glucose, GIP, gut GLI, insulin, and glucagon in pregnancy and postpartum in 11 normal women, 10 normal weight gestational diabetics, and 10 overweight gestational diabetics

	Normal women	Gestational diabetics		Difference between groups:		
		Normal wt	Overweight	1 and 2	2 and 3	1 and 3
	Group 1	Group 2	Group 3	P <	P <	P <
Glucose (mmol × l^{-1})						
Pregnancy	4.1 ± 0.1*	5.5 ± 0.3	5.6 ± 0.2	0.01	NS	0.01
Postpartum	4.7 ± 0.1	4.9 ± 0.1	5.3 ± 0.1	NS	0.05	0.01
P <	0.01	NS	NS			
GIP (pmol × l^{-1})						
Pregnancy	43 ± 10	46 ± 8	48 ± 6	NS	NS	NS
Postpartum	41 ± 2	39 ± 6	39 ± 7	NS	NS	NS
P <	NS	NS	NS			
Gut GLI (pmol-eqv × l^{-1})†						
Pregnancy	25 ± 2	28 ± 4	23 ± 2	NS	NS	NS
Postpartum	35 ± 3	27 ± 3	24 ± 1	NS	NS	0.05
P <	0.05	NS	NS			
Insulin (pmol × l^{-1})						
Pregnancy	90 ± 9	165 ± 29	251 ± 22	0.05	0.05	0.01
Postpartum	72 ± 5	79 ± 14	151 ± 22	NS	0.05	0.01
P <	0.05	0.01	0.01			
Glucagon (pmol × l^{-1})						
Pregnancy	16 ± 1	20 ± 4	15 ± 3	NS	NS	NS
Postpartum	13 ± 1	11 ± 2	11 ± 2	NS	NS	NS
P <	0.01	0.05	0.05			

* Mean ± SEM.
† In the gut GLI assay a pancreatic glucagon standard curve is used, the ensuing unit being pmol-equivalents of pancreatic glucagon × l^{-1}.

FIGURE 1. Changes in plasma concentrations of glucose, GIP, gut GLI, insulin, and glucagon in 11 normal women after oral glucose ingestion in pregnancy (open circles) and postpartum (closed circles). Values are mean ± SEM. Asterisks indicate significance of difference between findings in pregnancy and postpartum.

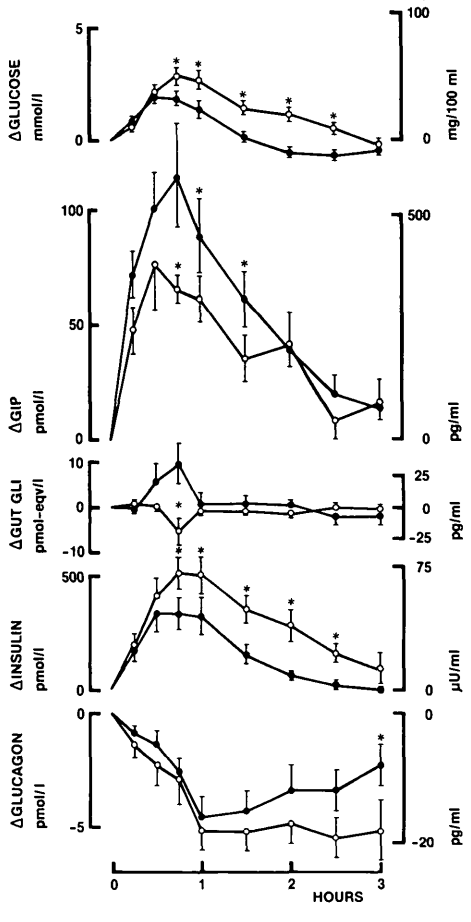
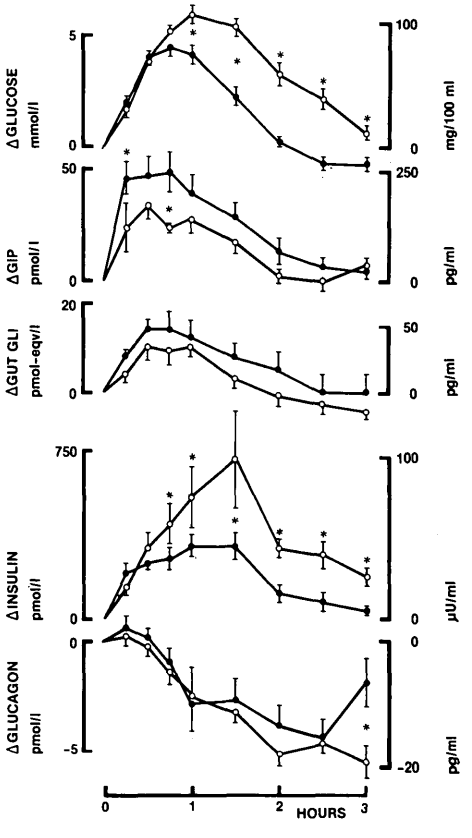


FIGURE 2. Changes in plasma concentrations of glucose, GIP, gut GLI, insulin, and glucagon in 10 normal weight gestational diabetics after oral glucose ingestion in pregnancy (open circles) and postpartum (closed circles). Values are mean ± SEM. Asterisks indicate significance of difference between findings in pregnancy and postpartum.



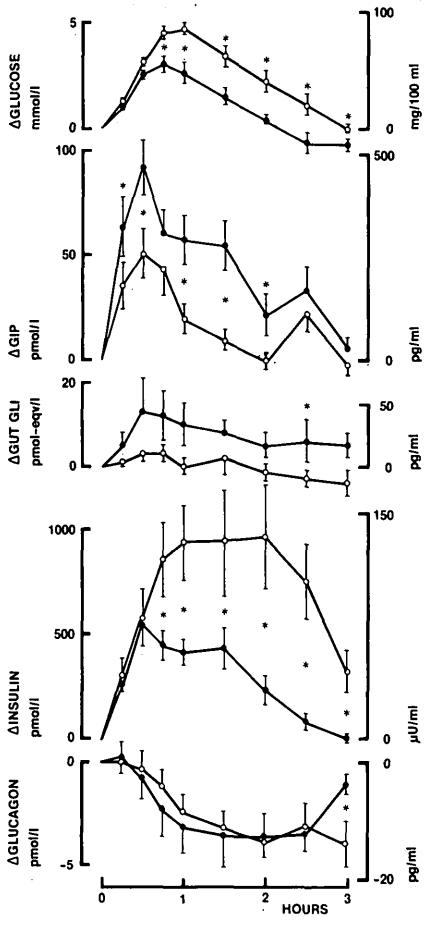


FIGURE 3. Changes in plasma concentrations of glucose, GIP, gut GLI, insulin, and glucagon in 10 overweight gestational diabetics after oral glucose ingestion in pregnancy (open circles) and postpartum (closed circles). Values are mean ± SEM. Asterisks indicate significance of difference between findings in pregnancy and postpartum.

partum, whereas GIP levels were lower in pregnancy than postpartum. In normal pregnancy, gut GLI concentrations did not increase after glucose ingestion in contrast to postpartum findings in normal women and findings in the gestational diabetics in both states. In the normal weight gestational diabetics, gut GLI levels were similar in pregnancy and postpartum, whereas in the overweight gestational diabetics, levels tended to be lower in pregnancy. The insulin response to glucose was increased in pregnancy in all three groups. In the normal women, the suppression of glucagon after glucose ingestion was slightly more pronounced and sustained in pregnancy than postpartum. Also, in both groups of gestational diabetics, glucagon concentrations at 180 min were lower in pregnancy than postpartum.

Integrated hormone responses. Table 3 shows the integrated hormone responses in pregnancy and postpartum in the three groups of women.

The GIP response to glucose was decreased in pregnancy in all three groups. Moreover, in pregnancy, both groups of gestational diabetics exhibited a smaller GIP response than observed in the normal women. Postpartum, only the normal weight gestational diabetics presented a reduced GIP response. Thus, postpartum the GIP response to glucose was higher in the overweight gestational diabetics than in the normal weight gestational diabetics.

The gut GLI response to glucose was diminished in pregnancy in the overweight gestational diabetics. In the two other groups, no effect of pregnancy was observed and no difference between the groups was detected.

In all groups the insulin response to glucose was increased in gestation. Both in pregnancy and postpartum the insulin response was greater in the overweight gestational diabetics than in either of the two other groups, whereas the responses were similar in the normal weight gestational diabetics and in the normal women.

The suppression of glucagon after glucose ingestion was more marked in pregnancy in the normal women, whereas

TABLE 3
Integrated responses of GIP, gut GLI, insulin, and glucagon to oral glucose ingestion in 11 normal women, 10 normal weight gestational diabetics, and 10 overweight gestational diabetics in pregnancy and postpartum

	Normal women	Gestational diabetics		Difference between groups: 1 and 2	2 and 3	1 and 3
		Normal wt	Overweight			
	Group 1	Group 2	Group 3	P <	P <	P <
GIP (pmol × 1^{-1} × min)						
Pregnancy	6859 ± 876*	2361 ± 427	3217 ± 868	0.01	NS	0.01
Postpartum	9947 ± 1366	4477 ± 554	7698 ± 1299	0.01	0.05	NS
P <	0.05	0.01	0.01			
Gut GLI (pmol-eqv × 1^{-1} × min)†						
Pregnancy	−138 ± 232	454 ± 259	−78 ± 345	NS	NS	NS
Postpartum	251 ± 602	1170 ± 464	1337 ± 575	NS	NS	NS
P <	NS	NS	0.05			
Insulin (pmol × 1^{-1} × min)						
Pregnancy	51,115 ± 4808	66,774 ± 12,723	123,912 ± 24,189	NS	0.05	0.01
Postpartum	24,552 ± 4034	33,380 ± 5284	49,513 ± 6957	NS	0.05	0.01
P <	0.01	0.01	0.01			
Glucagon (pmol × 1^{-1} × min)						
Pregnancy	−750 ± 121	−528 ± 71	−447 ± 121	NS	NS	NS
Postpartum	−479 ± 110	−328 ± 121	−520 ± 154	NS	NS	NS
P <	0.05	NS	NS			

* Mean ± SEM.

† In the gut GLI assay a pancreatic glucagon standard curve is used, the ensuing unit being pmol-equivalents of pancreatic glucagon × 1^{-1}.

no effect of pregnancy was seen in the gestational diabetics. Neither in pregnancy nor postpartum was any difference between the groups observed.

DISCUSSION

Both the normal pregnant women and the gestational diabetics exhibited an increased insulin response to glucose ingestion in pregnancy in agreement with previous findings.[3] Probably due to increased body weight,[23] the overweight gestational diabetics, in pregnancy as well as postpartum, displayed an insulin response to glucose ingestion approximately twice as large as that observed in the other two groups of women. In the normal women, the suppression of plasma glucagon levels after glucose ingestion was more marked in pregnancy than postpartum, whereas no effect of pregnancy was seen in the gestational diabetics. Previously, enhanced glucagon suppression in pregnancy has been described in gestational-diabetic as well as in normal pregnancy,[3] but the differences were small.

No effect of pregnancy on fasting GIP concentrations was found in any of the three groups investigated. However, in all three groups the GIP response to glucose was reduced in gestation. Diminished GIP response to oral glucose ingestion has been described in normal pregnancy,[16] whereas data on plasma GIP levels in gestational diabetic pregnancy have not previously been published. As GIP stimulates insulin secretion after oral glucose ingestion,[14] the impaired GIP response might contribute to the diabetogenicity of normal as well as gestational-diabetic pregnancy, in that an unaltered GIP response probably would have led to higher insulin levels. Whether this would have normalized glucose tolerance is, however, uncertain.

In pregnancy, the GIP response to oral glucose was considerably lower in both groups of gestational diabetics than in normal women. Postpartum, when glucose tolerance had returned to normal in all patients, the GIP response to glucose was still reduced in the normal weight gestational diabetics, whereas it was similar in the overweight gestational diabetics and in the normal women. Previously, the GIP response to glucose has been reported normal,[24] increased,[25,26] or decreased[27] in nonpregnant non-insulin-dependent diabetics. The reason for the diverging results is not clear, but it may be that the patients studied, including the gestational diabetics in the present investigation, constitute different subgroups of non-insulin-dependent diabetics.

Postpartum, the GIP response to glucose was lower in the normal weight gestational diabetics than in the overweight patients. This emphasizes the clinical impression of heterogenicity of the gestational diabetics.[1]

The reason for the reduced GIP response to oral glucose ingestion in pregnancy—whether normal or associated with gestational diabetes—is unknown. Delayed gastric emptying in pregnancy could be an explanation. However, there is no general agreement of the influence of pregnancy on the rate of gastric emptying.[28] Moreover, as judged by the glucose concentrations curves (Figures 1–3), glucose absorption was, at the most, marginally delayed in pregnancy. Finally, maximum GIP levels did not occur later in pregnancy than postpartum. It thus seems unlikely that delayed gastric emptying could explain the decreased GIP response to glucose in gestation.

The secretion of GIP is believed to be under a negative feedback control by pancreatic factors, as insulin[29–31] and C-peptide[32] seem to reduce the GIP response to fat ingestion. In the present study, impaired GIP secretion was found in the presence of high insulin levels and a feedback control of insulin on GIP secretion could explain the findings. However, such a feedback control does not seem to influence the GIP response to glucose[33–35] and the explanation for the reduced GIP responses in pregnancy and in gestational diabetics as compared with normal women thus remains unclarified.

Postpartum, the concentrations of gut GLI increased after glucose ingestion in all groups. In pregnancy, however, the increase was impaired in the overweight gestational diabetics and abolished in the normal women. The physiologic actions of gut GLI remain to be elucidated and the consequences of the reduced gut GLI levels in pregnancy are thus not clear. If, however, gut GLI[15] in addition to GIP[14] stimulates the insulin secretion after oral glucose intake, the impaired gut GLI responses might also contribute to the diabetogenicity of pregnancy.

In the present investigation, the overweight gestational diabetics were investigated earlier in pregnancy than the normal women (34 ± 1 versus 38 ± 1 wk, $P < 0.01$, Table 1), whereas no difference was found between the times of investigation postpartum. This difference is probably not important to the findings as it would tend to make the impact of pregnancy most pronounced in the normal women while the results, in contrast, showed the effect of pregnancy on insulin and GIP secretion to be most marked in the gestational diabetics.

This study demonstrates that pregnancy, whether normal or associated with gestational diabetes, is accompanied by marked changes in the secretion of gastrointestinal insulinotropic hormones after glucose ingestion. These findings might be important for the study of alterations of carbohydrate metabolism in pregnancy, but they may also have a bearing on the influence of pregnancy on gastrointestinal physiology.

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