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Genetic predictors of ondansetron effectiveness and recurrence risk for hyperemesis gravidarum

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BACKGROUND

Most women experience nausea and vomiting of pregnancy (NVP) and 18% require medication. The most severe form of NVP, hyperemesis gravidarum (HG) is associated with weight loss, undernutrition, and adverse maternal and child outcomes. Antiemetic effectiveness and risk of recurrence are major concerns. Ondansetron is the most effective antiemetic, but may be ineffective in ~40% of patients. Therefore, a subset of HG patients who do not respond to antiemetic treatments require total parenteral nutrition (TPN). In addition, recurrence risk is high – some studies show a higher than 80% risk of recurrence.

AIMS

- AIM 1: To identify genetic predictors of ondansetron effectiveness
- AIM 2: To identify genetic predictors of recurrence risk

METHODS

- Patients with HG provided DNA samples and reported treatments received, effectiveness, and recurrence of HG in a subsequent pregnancy.
- We investigated the association of selected germline polymorphisms with 1) ondansetron response and 2) recurrence risk in patients with HG
- Odds ratios and corresponding p-values were calculated using standard methods. A cutoff of $p<0.05$ was considered significant.
- Ondansetron effectiveness: Polymorphisms in pharmacogenetic modifiers of ondansetron (*ABCB1, CYP2D6, HTR3C, HTR3B*) were analyzed for association with self-reported ondansetron effectiveness.
- Recurrence: Participants who were genotyped and reported a diagnosis of HG treated with IV fluids in their first pregnancy and reported HG with >5% weight loss from pre-pregnancy weight in their second pregnancy were defined as having a recurrence. HG risk locus *PGR_TRPC6* was analyzed for association with recurrence.

RESULTS

- 58% (239/413) of HG patients reported ondansetron was effective.
- Patients who reported ondansetron was effective were significantly less likely to be treated with TPN (p=0.0012) than patients who reported it was ineffective.
- No associations were found between the *ABCB1, CYP2D6, HTR3C, HTR3B* variants tested and self-reported effectiveness of ondansetron.
- 82% (116/142) of participants with two pregnancies had a recurrence.
- More patients with a recurrence required TPN (15.5% vs 7.7%), but the difference was not statistically significant (p=0.31)
- rs59743346 in *TRPC6* was a significant predictor for recurrence of HG (OR=9.1, p=0.001, CI=2.3-35.0).
- Homozygosity for the minor allele was identified in only 3% of recurrences compared to 23% of cases that did not recur.

Patient Demographics and Disease Severity

	n	European descent	HG treated with IV	HG treated with TPN
Ondansetron effective	239	89.96%	90.38%	9.62%
Ondansetron ineffective	174	88.51%	78.74%	21.26%
HG recurrence	116	91.38%	84.48%	15.52%
HG non-recurrence	26	96.15%	92.31%	7.69%

No association between pharmacogenetic modifiers of ondansetron and effectiveness

	ABCB1 rs2032582	ABCB1 rs2032582	HTR3C rs6766410	HTR3B rs2276307	ABCB1 rs1045642	CYP2D6 rs1065852	CYP2D6 rs16947
	GG+AG vs AA	AA+AT vs TT	CC+CA vs AA	AA+AG vs GG	AA+AG vs GG	GG+GA vs AA	GG+GA vs AA
Odds Ratio	0.73	1.41	1.28	1.17	0.92	0.70	0.57
p-value	0.21	0.87	0.34	0.67	0.74	0.56	0.07

rs59743346 associated with recurrence risk

TRPC6
rs59743346

	Recurrence		Non-recurrence	
Genotype	AAG/AAG + AAG/del	del/del	AAG/AAG + AAG/del	del/del
n	121	4	20	6

Odds ratio: 9.08 **95% CI: 2.35 – 35.03** **p=0.001**

SUMMARY / CONCLUSION

- The association between those reporting ondansetron ineffectiveness and their treatment with TPN validates self-reporting of effectiveness.
- The variants tested did not predict ondansetron effectiveness, although rs16947 came close (p=0.07), so a larger sample size may result in different findings.
- Those with more severe disease (requiring TPN treatment) were more likely to have a recurrence, but the results were not statistically significant, so a larger sample size may result in different findings.
- We found that rs59743346, in addition to previously identified *GDF15* polymorphism rs16982345, may be useful in predicting recurrence risk.
- This work has implications for elucidating the biology of HG, counseling, diagnosis, and treatment.

REFERENCES

Fejzo et al., et al. “Nausea and vomiting of pregnancy and hyperemesis gravidarum.” Nature reviews. Disease primers vol. 5,1 62 (2019).

Fejzo et al., “Evidence GDF15 Plays a Role in Familial and Recurrent Hyperemesis Gravidarum.” Geburtshilfe und Frauenheilkunde vol. 78,9 (2018)

Fejzo et al., “Placenta and appetite genes GDF15 and IGFBP7 are associated with hyperemesis gravidarum.” Nature communications vol. 9,1 1178. 21 Mar. 2018,

Fejzo et al., “Antihistamines and other prognostic factors for adverse outcome in hyperemesis gravidarum.” European journal of obstetrics, gynecology, and reproductive biology vol. 170,1 (2013): 71-6.

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CONTACT INFORMATION / CONFLICT OF INTEREST

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